[redacted]

TI: S. Cragg
NM: R. Allison

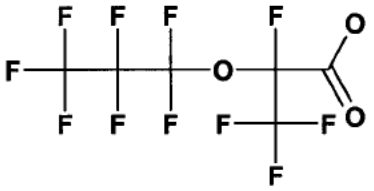
SAT Date: 7 July 2008
RAD RA: 1 October 2008

STANDARD REVIEW RISK ASSESSMENT
FOR P08-0508 & P08-0509

BACKGROUND

PMN P08-0508 and P08-0509, submitted by DuPont Fluoroproducts on 31 July 2008, are the free acid and ammonium salt of perfluorinated propanoic acid linked via an ether bond to perfluorinated propane. These two PMN's have the molecular structures, Chemical Abstract Service names, and CAS Numbers shown below.

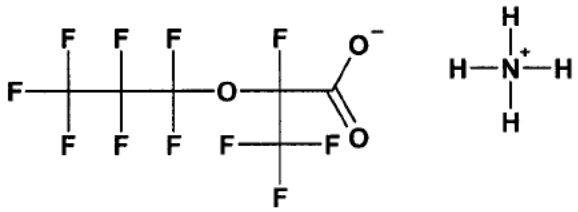
P08-0508



[redacted]

Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-
(CAS# 13252-13-6)

P08-0509



Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-,
ammonium salt (1:1)
(CAS# 62037-80-3)

P08-508, which will be manufactured in the U.S., is a [redacted] at room temperature with a molecular weight of 330. It as an estimated water solubility of 205 mg/L with expected rapid migration to groundwater and estimated ultimate biodegradation on the order of months. The PMN has an estimated boiling point of 173°C, a measured vapor pressure of [redacted], estimated log Kow of 3.66, estimated log Koc of 2.08, and an estimated fish BCF of 0.50. P08-509, the ammonium salt of the PMN, is [redacted] at room temperature with a molecular weight of 347. It is estimated to be dispersible in water with expected rapid migration to groundwater and estimated ultimate biodegradation on the order of months. The PMN has an estimated boiling point > 400°C, an estimated vapor pressure < 0.000001 mmHg at 25°C, estimated log Kow of 0.78, estimated log Koc of 2.91, and an estimated fish BCF of 0.50. Other physico/chemical values for both PMN's, estimated or

measured, are included in the attached Structure Activity Report (see appendices).

This acid PMN (P08-508) is intended [redacted] and for [redacted] polymerization aid ([redacted]. The ammonium salt (P08-509) is intended for use as a [redacted] as a polymerization aid to [redacted]. The submitter maintains that the PMN [redacted] from a health, fate and environmental effects standpoint. The toxicity information provided by the submitter for the ammonium salt (P08-509) shows some toxicity in two oral gavage 28-day studies conducted with rats and mice. Other perfluorinated alkyl ether analogs that are similarly short in chain-length also show toxicity [redacted]. A longer chain-length perfluorinated alkyl ether analog [redacted], showed liver, lung and reproductive/developmental effects at very low doses (e.g., < 1 mg/kg-day). For these reasons, the present PMN's are undergoing standard review and their health and environmental effects are summarized below.

TOXICITY ASSESSMENT

Full reports of the discipline experts are included in the appendix.

Submitted Health Data for the PMN:

Toxicokinetics: (L. Keifer)

Absorption of either PMN via lung and G.I. is assumed to be good (100%). Absorption via skin was determined in vitro with rat and human skin and expressed as a flux. Values are reported in the appendix for this discipline. For purposes of this risk assessment, absorption via the skin is also assumed to be 100%. Both the free acid and ammonium salts were subjected to pharmacokinetic studies (single gavage doses of non-radiolabeled PMN at 10 or 30 mg/kg) in rats and monkeys. In rats, females cleared either PMN substantially faster than males. Only urinary excretion was measured. T1/2's were not reported in the rat studies. In monkeys, sex differences were not evident regarding clearance rates.

Systemic Toxicity: (L. Anderson)

Systemic toxicity is evaluated in two reviews (appended). The first review evaluates acute toxicity studies for both PMN's and the second review evaluates 28-day gavage studies in rats and mice. In summary, both PMN's have low acute toxicity by inhalation, oral, or dermal routes of exposure. Necrosis was reported in an eye irritation study with rabbits for the ammonium salt although skin irritation was reported as slight to moderate with rabbits.

In a repeated dose study with rats, P08-509 (ammonium salt) was administered on 28 consecutive days via gavage to (10/sex/dose level). Male rats received doses of 0, 0.3, 3, or 30 mg/kg-day while females received 0, 3, 30, or 300 mg/kg-day. Additional control and high dose groups also, comprised of 10 rats/sex/dose, were sacrificed 29 days after the last treatment in order to evaluate the reversibility of any toxic effects found immediately post-dosing. Monitored

toxicity endpoints included: mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology. Cytochrome P-450 content and beta-oxidation activity in the liver also were evaluated.

All animals survived. Clinical signs were confined to high-dose females (300 mg/kg-d) where urogenital staining was reported. Hematological evaluation revealed decreased red blood cell count, decreased hemoglobin/hematocrit and increases in absolute reticulocyte counts in males given 3 or 30 mg/kg-day. Clinical chemistries revealed alterations in males and females consistent with liver injury. Liver and kidney weights were increased variously in males and females in a dose response manner. For males, a LOAEL of 3 mg/kg-day and NOAEL of 0.3 mg/kg-day was determined based on hematology findings, organ weights and liver effects.

In a repeated dose study with mice, (10/sex/dose) received 0, 0.1, 3, or 30 mg/kg-day of P08-509 for 28 consecutive days via gavage. Additional negative controls and high dose animals were evaluated for reversibility of effects 28 days after the last treatment. As with rats, decreases in red blood cells counts, hemoglobin and hematocrits were reported at 3 and 30 mg/kg-day. Also similar to rats, increase liver weights were found along with increases in adrenal weights. Other findings are reported in the appendix. A LOAEL 3 mg/kg-day and a NOAEL of 0.1 mg/kg-day is concluded based on organ weight changes observed at 3 mg/kg-day accompanied by histopathology.

Immunotoxicity: (R. Ward)

The PMN was not tested specifically for immunotoxicity. However, PFOA has toxic effects on the thymus and spleen, which indicates immunotoxic potential for the PMN. In a 90-day repeated dose study with rats, [redacted] also showed toxic effects to immunologically active organs at low doses (LOAEL = 0.5 mg/kg-d; NOAEL 0.13 mg/kg-day).

Genotoxicity: (M. Cimino)

Based on data on the PMNs themselves and on analogues, P08-508 and P08-509 are or may be: (a) not gene mutagens in two species of prokaryotes; (b) chromosome mutagens in mammalian and human cells in culture, but not in mammals *in vivo* and; (c) not inducers of DNA effects in mammalian cells *in vivo*.

The positive data on the PMN for *in vitro* chromosomal aberrations in mammalian and human cells are of some concern. However, the negative responses for *in vivo* chromosomal effects as micronuclei and as chromosomal aberrations, and for induction of DNA effects, alleviate that concern. There is no basis for recommending additional mutagenicity testing for the PMNs, and there is little support for a cancer concern based upon mutagenicity. The lack of mutagenicity concern does not negate a cancer concern should such concern be based upon nongenotoxic information.

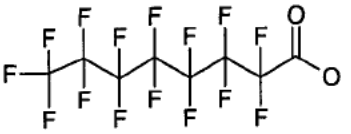
Carcinogenicity: (Y. Woo)

The carcinogenic potential of the PMN is uncertain because the carcinogenic potential of PFOA and other PFOA-like analogs is uncertain. Although rodents administered PFOA develop liver tumors, Leydig cell tumors of the testis, and acinar cell tumors of the pancreas, the liver tumors are mediated by peroxisome proliferation not thought to be operative in humans. Similarly, the estrogenic effects of PFOA are believed to mediate Leydig cell tumor development by mechanisms also of questionable relevance to humans. The mechanism of pancreatic acinar tumor development in rodents has not yet been delineated; however, such tumors are rare in humans. Thus, the PMN is not assumed to be carcinogenic to humans.

Submitted Health Data for the Analogs [redacted] Several mammalian and ecotoxicity studies as well as some fate data were submitted for [redacted]. Mammalian toxicity tests indicated high toxicity, comparable to the perfluorinated alkyls. After standard review, it was concluded that these analogs did not offer a human health advantage with regard to lower toxicity over the perfluorinated alkyl analogs presently in commerce. [redacted] toxicities included internal organ damage (liver and lungs), organ weight changes (liver, kidney, spleen, testes, thymus, & adrenals), peroxisome proliferation, clinical chemistry changes at doses as low as 0.13 and 0.5 mg/kg-day in a 90-day oral study in rats with the ammonium salt form of the PMN. The NOAEL for this study was 0.03 mg/kg-day. Effects at these very low doses indicate high toxicity. The free acid also is severely irritating to eyes and skin. Finally, fluorotelomers of this molecular weight range (e.g., PFOA) have shown the potential for reproductive toxicity, which was not evaluated for these two analogs. The molecular structure of this analog is shown below.

[redacted]

PFOA Toxicity Data: Particularly the reproductive/developmental toxicity evaluation (SRC) focuses on PFOA. This evaluation is contained in the SRC review for reproductive and developmental effects. This review concludes a LOAEL of 1 mg/kg-day for systemic toxicity (decreased mean body weight, increased absolute and relative liver weights in F1 generation males) in a 2-generation reproductive toxicity assay and for reproductive effects (increased incidences of enlarged fontanel and reduced ossification of calvaria in pups) in a rat developmental toxicity assay. References are given in the full SRC review. The molecular structure of PFOA is shown below.



Pentadecafluoroocantoic Acid
(a.k.a. perflourooctanoic acid or PFOA)
(CAS# 335-67-1)

EXPOSURE ASSESSMENT (HUMAN HEALTH)

Because release of the PMN to the environment will be restricted, exposure to the public is assumed to be negligible. Thus, only occupational exposures are considered in this risk assessment. Oral exposures are considered negligible in an occupational setting.

For occupational exposures, Table 1 shows the doses and margin of exposure calculations for occupational exposures for P08-508. [redacted], inhalation and dermal routs of exposure are evaluated. Table 2 shows doses and margins of exposure calculations for P08-509. Because the vapor pressure of the ammonium salt form of the PMN (P08-509) is negligible, inhalation exposures have not been calculated. Although a salt, in a liquid slurry solution (as assumed in the use scenarios), the P08-509 may be absorbed dermally at a rate assumed to be 25% of inhalation or oral routes. Absorption by oral and inhalation routes of exposure is assumed to be good and to be equivalent to each other. Consequently no adjustment for absorption differences is assumed between these two routes of exposure.

WORKER EXPOSURE: (M. El-Zoobi; Engineering Exposure Report using the ChemSteer Program)

PMN Manufacture: The PMN's will be manufactured [redacted] to be determined. The use scenarios are shown in Tables 1 & 2 for P08-508 and P08-509, respectively, along with estimated doses. Worker activities evaluated for P08-508 during manufacturing operations are [redacted]. Doses are calculated for inhalation and dermal routes of exposure. For P08-509, inhalation is assumed negligible due to low vapor pressure.

PMN Use: The PMN use scenarios are shown in Tables 1 and 2 along with estimated doses. For P08-508, using the PMN as a [redacted] intermediate, [redacted]. For P08-509, [redacted]

PMN Exposure to the General Public: Exposure to the public ([redacted]) has

been modeled using the EFast exposure assessment models. This model estimates a Lifetime Average Daily Dose (LADD) of 0.00481 mg/kg-day (see EFAST appendix).

RISK CHARACTERIZATION (HUMAN HEALTH)

Risk calculations in the form of margins of exposure (MOE's) are shown in Tables 1 and 2 for P08-508 and P08-509, respectively. Since the PMN substances are not considered to be carcinogenic, no cancer risks are calculated in this assessment. Non-cancer risk is assessed by comparing the estimated dose derived from the exposure assessment to the reference dose (i.e., the NOAEL of 0.1 mg/kg-day in this case). When a NOAEL is used as the reference dose, it must exceed the estimated dose by a factor of 100, i.e., the MOE must be at least 100.

CONCLUSIONS: Tables 1 and 2 show that some of the dermal and inhalation occupational exposures far exceed acceptable levels. Estimated exposures indicate unacceptable MOE's. Exposures would have to be reduced markedly to prevent over-exposure. In addition, the LADD from fugitive emissions estimated for population exposure (0.00481 mg/kg/d) is less than the NOAEL (0.1 mg/kg-d) by only a factor of 5 (MOE is 21). Thus, exposure of the general public [redacted] exceeds acceptable levels.

UNCERTAINTIES: The assumptions used in this risk assessment are conservative, intentionally erring on the side of protecting health when more accurate estimates cannot be made. These assumptions are inherent in the ChemSteer exposure model. For example, fugitive emissions are assumed to occur all at the same time which may not be the case. Assumptions are also conservative in the EFast model that uses ChemSteer output values. An example of conservative assumptions used in the EFast Model are the adding together of all fugitive air emissions and assume worst-case height of release (higher release elevations might mitigate downwind concentrations).

ECOTOXICITY ASSESSMENT

Ecotoxicity information was available for these two PMN's. No toxicity occurred in fish (rainbow trout), daphnia, or algae at concentrations up to 100 mg/L. In addition, ecotoxicity was predicted using ECOSAR, an EPA predictive model that estimates toxicity to fish, daphnia, and algae based on chemical categories and physico-chemical parameters specific to the PMN. ECOSAR predicted the toxicity for these PMN's based on a category of chemicals known as anionic surfactants of C8 chain-length and with a carboxylic acid functional group. Physico-chemical values used in the predictions were: solubility = 43 mg/L at 25C for P08-508, dispersivity in water for P08-509, pH 7, water hardness < 180 mg/L as CaCO3, and total organic carbon < 2.0 mg/L. ECOSAR predictions were in approximate agreement with the actual test data. From the test data, a concentration of concern of 1,000 µg/L (ppb) was assigned by dividing 100 mg/L by a factor of 10 to simulate a chronic effect level, then dividing again by another assessment (uncertainty) factor of 10, which yields a chronic Concentration of Concern (CoC) value of 1 mg/L or 1,000 µg/L (ppb). To derive an acute CoC, 100 mg/L is divided by a

factor of 5, yielding 20 mg/L or 20,000 µg/L. Guidance for deriving EPA concentrations of concern is described in "Interpretive Assistance of Sustainable Futures Summary Assessment" (August 2007).

EXPOSURE ASSESSMENT (ECOLOGICAL)

Surface water concentrations were estimated using EPA's predictive model, EFast (see appendix). EFast shows that the highest average concentration (7Q10) was approximately 166 µg/L for multiple scenarios.

RISK CHARACTERIZATION (ECOLOGICAL)

Because the maximum predicted stream concentration was below the chronic CoC of 1,000 µg/L and did not exceed this value any day of the year, the risk of chronic toxicity to the aquatic environment is low. Because none of the predicted stream concentrations approached the acute CoC of 20,000, the risk of acute toxicity to the aquatic environment is low.

RECOMMENDATIONS:

HEALTH TESTING RECOMMENDATIONS

Because the PMN is analogous to alkylperfluorinated carboxylic acid counterparts ([redacted]), reproductive toxicity testing (modified OECD 421) is recommended for [redacted] These analogous homologue alkyl perfluoro acids have been shown to be reproductively toxic in the past. As adjuncts, neurobehavioral (e.g., FOB, motor activity) and immunological testing (anti-sheep RBC response) should be conducted on additional animals in selected dose groups.

The existing toxicokinetics study with rats indicates some dissimilarity between the sexes but not as marked as for PFOA. Therefore, the reproductive toxicity test may be conducted with the rat.

Study	Guideline
1-Generation reproduction/developmental study	OECD 421, modified

The modifications for the 1-generation reproduction study (OECD 421, modified) test are: (1) increase the parental sample size to 20, (2) the duration of the study should be extended to until the pups have reached sexual maturation, (3) parental males should be dosed for 10 weeks prior to mating; (4) dosing of the parental animals should be continued through lactation and then the pups should be directly dosed until they reach sexual maturation; (5) pup body weight should be recorded on lactation days 0, 4, 7, 14, and 21 and then at weekly intervals; (6) litter size can be standardized to 4 pups/litter on lactation day 4 (optional); (7) at weaning one pup/sex/litter can

be randomly selected to follow until sexual maturation; and (8) the time of sexual maturation should be recorded (i.e. vaginal opening and preputial separation).

A two-year chronic toxicity/oncogenicity test is recommended (OPPTS 870.4300 /OECD 453), depending on intended production volumes and testing costs.

P-CHEM AND FATE TESTING RECOMMENDATIONS

The following physicochemical and environmental fate testing is recommended.

P-Chem Properties Testing	
UV/visible absorption	OPPTS 830.7050
Hydrolysis as a function of pH	OPPTS 835.2130
Environmental Fate Testing	
SCAS Test for Insoluble and Volatile Chemicals	OPPTS 835.5045
Aerobic and Anaerobic Transformations in Soil	OECD 307
Aerobic and Anaerobic Transformations in Aquatic Sediment systems	OECD 308
Direct Photolysis in Water	OPPTS 835.2210
Indirect Photolysis Screening Test	OPPTS 835.5270
* Phototransformation of Chemicals on Soil Surfaces	OECD Jan. 2002 Draft
Simulation test-Aerobic Sewage Treatment (Activated Sludge Units)	OECD 303A
Anaerobic biodegradability of organic compounds in digested sludge: measurement of gas production	OECD 311
Fish Bioconcentration Factor	OPPTS 850.1730

ECOTOXICITY TESTING RECOMMENDATIONS

At this time, potential risks to the aquatic environment appear to be acceptable.

RECOMMENDATIONS FOR EXPOSURE MITIGATION FOR HUMAN HEALTH

Based on the MOE's calculated in this assessment, personal protective equipment is recommended that would reduce inhalation exposures by at least 3,000-fold. Supplied air or self-contained breathing apparatus should be used during use scenarios to prevent exposures.

For possible dermal exposure to the PMN, skin exposure should be completely prevented by

wearing protective gloves impervious to penetration by the PMN substance. Other parts of the body that may be exposed to the PMN substance also should be similarly protected from exposure.

CALCULATION OF NEW CHEMICAL EXPOSURE LIMIT (NCEL)

Oral NOAEL = 0.1 mg/kg-day (Based on the 28-day mouse study)

divided by 100 = 0.001 mg/kg-day ← this is the "acceptable intake" on a per kilogram body weight basis

x 70 Kg (average adult body weight) = 0.070 mg/day ← "acceptable intake on a individual person basis

To convert from oral to inhalation exposure:

Assume average worker inhales 10 m3/work day

0.07 mg/day divided by 10 m3/day = 0.007 mg/m3 as the acceptable occupational exposure limit

= 7 micrograms/m3

The submitter could show that 7 ug/m3 is met by analytical monitoring. Also, the American Conference of Governmental Industrial Hygienists (ACGIH) has established an 8-hour Time Weighted Average (TWA) Threshold Limit Value (TLV) of 10 μg/m3 for ammonium perfluoroocatanoate (CAS# 3825-26-1), which is the ammonium salt of PFOA. This TLV could serve as an alternative to the NCEL calculated above.

REFERENCES

ChemSTEER (Chemical Screening Tool for Exposures and Environmental Releases). Screening Model for estimating occupational exposure and environmental releases of manufactured chemicals. Office of Pollution Prevention and Toxics, Chemicals Engineering Branch, Washington, D.C. May 4, 2004 Beta version.

EFAST (Exposure and Fate Assessment Tool Version 2). U.S. EPA publicly available predictive model used to estimate media concentrations of chemical released into the environment.

FIFRA SAP (2004). Transmittal of meeting minutes of the FIFRA Scientific Advisory Panel meeting held December 9, 2003. Memorandum from S.M. Knott to J.J. Jones and C.M. Auer, March 5, 2004. Office of Science Coordination and Policy, U.S. Environmental Protection Agency, Washington, D.C.

TABLE 1: PMN Dose & MOE Calculations for P08-0508 (Occupational Exposures)

(using the NOAEL from a rat oral 28-day study with the ammonium salt form of the PMN)

[redacted]

Wednesday, 1 October 2008

Occupational Exposures	Per Day Dose* (mg/day)	Absorption Factor**	Ave Adult BW (kg)	PMN Dose (mg/kg-d)	NOAEL Dose (mg/kg-d)	Margin of Exposure "MOE"
[redacted]						

* Values in this column are taken directly from the engineering report using the "ChemSteer" exposure model.

** The PMN absorption factor is assumed equivalent between the oral and inhalation routes of exposure (good absorption by both routes). Compared to the oral route of exposure, dermal exposure is assumed to be poor. A correction factor of 0.25 (based [redacted]) is applied to the dermal estimated exposure to compare to the oral NOAEL.

TABLE 2: PMN Dose & MOE Calculations for P08-0509 (Occupational Exposures)

(using the NOAEL from a rat oral 28-day study)

[redacted]

Wednesday, 1 October 2008

Occupational Exposures	Per Day Dose* (mg/day)	Absorption Factor**	Ave Adult BW (kg)	PMN Dose (mg/kg-d)	NOAEL Dose (mg/kg-d)	Margin of Exposure "MOE"
[redacted]						

* Values in this column are taken directly from the engineering report using the "ChemSteer" exposure model.

** The PMN absorption factor is assumed equivalent between the oral and inhalation routes of exposure (good absorption by both routes). Compared to the oral route of exposure, dermal exposure is assumed to be poor. A correction factor of 0.25 (based [redacted]) is applied to the dermal estimated exposure to compare to the oral NOAEL.

Appendices

STRUCTURE ACTIVITY TEAM REPORT [redacted] 07/11/08

CASE NUMBER: **P08-0508/0509**

RELATED CASES: [redacted]

CONCLUSIONS/DISCUSSIONS

TYPE OF CONCERN:	HEALTH	ECOTOX
LEVEL OF CONCERN:	2-3	2

KEYWORDS: MUTA IRR/CORR-E,MM,L,S
LIVER BLOOD KIDNEY
HEART LUNG ONCO
AQUATOX

SUMMARY OF ASSESSMENT

FATE: **0508**: [redacted] (E)
log Kow = 3.66 (E);
S = 205 mg/L at 25 °C (E)
[redacted]
BP = 173 °C (NOMO5) based [redacted]
H = 2.05E-4 (E)
log Koc = 2.08 (E)
log Fish BCF = 0.50 (E)
POTW removal (%) = 0
Time for complete ultimate aerobic biodeg > mo
Sorption to soils/sediments = low
Volatilization half-life from a standard river = 7 hrs
Volatilization half-life from a standard lake = 10 da
Atmospheric Oxidation Half-life = 250 hr via OH radical
PBT Potential: P3B2T3
*CEB FATE: Migration to ground water = rapid

0509: Estimations for the covalent ion pair MW 347 $C_6H_4F_{11}NO_3$
Solid with MP = 127 °C (E)
log Kow = 0.78 (E);
S = Disp./1.4 g/L at 25 °C (ICB/E)
VP < 1.0E-6 torr at 25 °C (E)
BP > 400 °C (E)
H < 1.00E-8 (E)
log Koc = 2.91 (E)
log Fish BCF = 0.50 (E)
POTW removal (%) = 0; OECD111(Hydrolysis): t1/2(pH4,7,9 at 50C): >1yr (0%/5d); OECD301B(Mod Sturm CO2 ev): 0%/28d.
Time for complete ultimate aerobic biodeg > mo

Sorption to soils/sediments = low
PBT Potential: P3B2T3
*CEB FATE: Migration to ground water = rapid

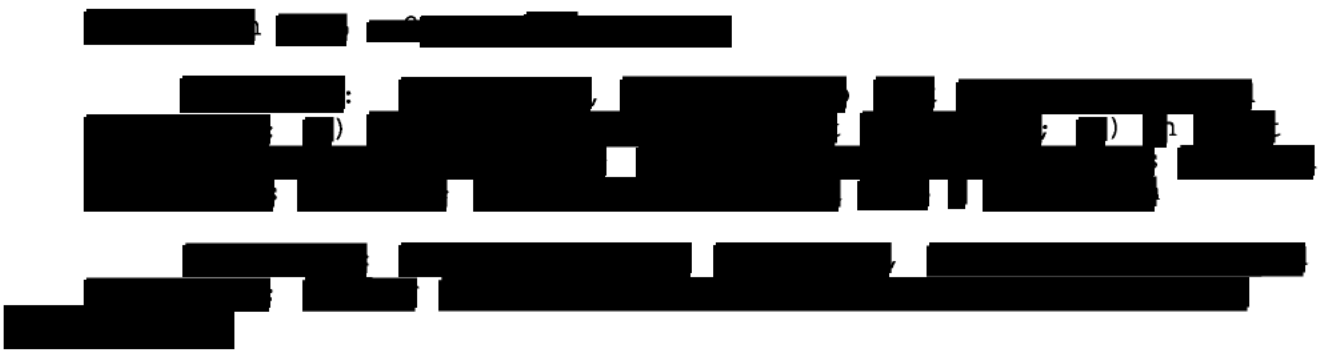
HEALTH: **0508**: Absorbed all routes (analog). **0509**: Expect poor absorption from the skin, good absorption from the lung and GI tract (analog). Concern for mutagenicity; liver, blood, kidney, and heart toxicity; corrosion to all tissues (508), dermal sensitization (508) based on submitted test data; and lung toxicity (509) based on surfactant properties. Concern for oncogenicity based on C_6 and C_8 perfluoroacids.

*CEB HEALTH: Moderate high concern (Dermal, inhalation, drinking water, fish ingestion)

Test data: **0508**: (-) Salmonella with and without activation; (-) E. coli with and without activation; (+) for chromosome aberrations in CHO cells with and without activation for polyploidy; (-) for chromosome aberrations in CHO cells with and without activation for structural changes; rat oral LD_{50} = 550 mg/kg (F); corrosive to skin using the *in vitro* Corrositex assay; rat clearance time following oral administration: 28 (M) & 8 (F) h at 10 mg/kg, 22 (M) & 4 (F) h at 30 mg/kg; rats dosed orally at 30 mg/kg for 7 days had increased liver weight and liver toxicity; rat 14-day oral LOEL = 30 mg/kg, liver, blood, and kidney toxicity; (+) for skin sensitization in mice using the local lymph node assay with EC_3 = 37%; no metabolism by rat hepatocytes *in vitro* in 2 h

0509: (-) Salmonella with and without activation; (-) E. coli with and without activation; (+) for chromosome aberrations in CHO cells with and without activation for crude material, (+) with activation for a purified material for structural changes; equivocal (+) for chromosome aberrations in CHO cells with and without activation for polyploidy; (-) in an oral mouse micronucleus assay; (-) in a rat hepatocyte UDS assay *in vitro*; (-) in a mouse *in vivo* chromosome aberrations assay; (-) in an *in vivo* rat UDS assay; no skin irritation in rabbits; mouse oral LD_{50} = 1030 mg/kg (F); rat oral LD_{50} = 1750 mg/kg (M), 3129 mg/kg (F); rat oral ALD = 7500 mg/kg, liver toxicity; rabbit dermal LD_{50} >5000 mg/kg, necrosis of skin; rat dermal LD_{50} >5000 mg/kg, necrosis of skin; rat clearance time following oral administration: 12 (M) & 4 (F) h at 10 mg/kg, 22 (M) & 8 (F) h at 30 mg/kg; mice dosed orally for 7 days with 30 mg/kg had increased liver weight and liver toxicity; rat 14-day oral LOEL = 30 mg/kg with blood, liver, kidney, and heart toxicity; no skin sensitization in mice using the local lymph node assay

[redacted]



P08-0088: negative in Salmonella and E coli
uncertain positive for chromosome aberrations in CHL cells, positive results seen at the threshold of or beyond the point of cytotoxicity
28-day oral study in rats - NOEL = 5 mg/kg; hematological findings and changes in blood chemistry at 100 mg/kg; effects on the liver , kidneys, and forestomach at 100 mg/kg; increased kidney weights at 25 and 100 mg/kg
pharmacokinetic study in rats, iv administration - systemic exposure was 7 times higher in males than females; serum half-life = 9.4 hours in females and 5.4 hours in males
pharmacokinetic study in monkeys, iv administration - pharmacokinetic parameters in serum were similar between genders; males appeared to have a higher exposure and longer half-life than females
acute oral study in rats - LD50 = 500 mg/kg

ECOTOX: Predicted (P) and measured (M) toxicity values in mg/L (ppm) are:

fish 96-h LC50	=	60.0	P
fish 96-h LC50	>	96.9	M, O mykiss
daphnid 48-h LC50	=	47.0	P
daphnid 48-h LC50	>	102	M
green algal 96-h EC50	=	12.0	P
green algal 72-h EC50	>	106	M
fish chronic value	=	9.0	P
daphnid ChV	=	7.0	P
algal ChV	=	6.0	P

Predictions are based on SARs for anionic surfactants; SAR chemical class = surfactant - anionic - COO - C8; MW 330; [redacted] S = 43 mg/L at 25 C (P,508)/dispersible in water (P,509); pH7; effective concentrations based on 100% active ingredients and mean measured concentrations; hardness <180.0 mg/L as CaCO3; and TOC <2.0 mg/L;
moderate concern for toxicity;
assessment factor = 10.0
concern concentration = 1.0 mg/L (ppm)
*CEB ECOTOX: All releases to surface water with CC = 1000 ppb
SAT Co-chair: Leonard Keifer 564-8916

MEMORANDUM

SUBJECT: Absorption Standard Review and Study Reviews for PMN 08-508/509

FROM: Leonard C. Keifer, Ph.D., FAIC
Chemist
New Chemicals Screening and Assessment Branch
Risk Assessment Division (7403M)

TO: Steve Cragg, Ph.D., DABT
Technical Integrator
New Chemicals Screening and Assessment Branch
Risk Assessment Division (7403M)

THRU: Robert E. Morcock, Ph.D., Chief
New Chemicals Screening and Assessment Branch
Risk Assessment Division (7403M)

[redacted]

I. INTRODUCTION

PMN substance 08-508, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoic acid (CAS No. 13252-13-6, Figure 1), is a [redacted] with a molecular weight of 330, a boiling point of [redacted] (PMN submission), an estimated water solubility of 43 mg/L, and an estimated log K_{ow} of 8.12 (SAT Report).

PMN substance 08-509, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoic acid ammonium salt (CAS No. 62037-80-3, Figure 1), is a solid with a molecular weight of 347, it is dispersible in water (SAT Report).

II. CONCLUSIONS

A. Absorption: Absorption of the PMN substances through the skin is expected to be poor although extent of absorption may be increased by the acidity (508) or surfactant properites (509) of the compounds. Absorption from the lung and GI tract is expected to be good.

Estimated percent absorbed:
SKIN: 6.2 $\pm$ 5.3 $\mu g/cm^2/h$ (human); 70 $\pm$ 5.3 $\mu g/cm^2/h$ (rat)
LUNG: 100%
GI TRACT: Unknown

B. Metabolism: Over short residence time no metabolism of the PMN substances is expected.

III. BASES FOR CONCLUSIONS

A. Absorption:

1. Skin: The submitter provided an *in vitro* study (see below; [redacted] investigating the dermal penetration of PMN substance 509 through human and rat skin, results as indicated above.

2. Lung: Water-soluble compounds with molecular weights in the range of 300 to 1,400 [e.g., sucrose, MW = 342, and cyanocobalamin (Vitamin B_{12}), MW = 1,355] and with low lipid solubility are absorbed from the lung (half-life 84 to 190 min in adult rats, (Schanker and Hemberger, 1983).

3. GI Tract: When pregnant rats were dosed via oral gavage with [redacted] (dose not reported) a maximum maternal blood level of 20 µg/mL was measured at 4 hours post dosing [redacted]. Sufficient information was not available from this study to determine the extent of absorption.

B. Metabolism: The submitter provided an *in vitro* study (see below; [redacted]) investigating the metabolism of PMN substance 509 by liver microsomes. No apparent loss of parent compound was noted.

IV. REVIEW OF STUDY FOR PMN SUBSTANCE 508

A. Pharmacokinetics in rats

Groups of 3 male and 3 female rats were dosed via single oral gavage with either 10 or 30 mg/kg of PMN substance 508 (98%). Blood samples were taken before dosing and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after dosing. In addition fat and liver samples were taken at terminal sacrifice. Samples were analyzed for parent compound suing HPLC/MS with a level of quantitation (LOQ) of 20 ng/mL [redacted]

Clearance times for PMN substance 508 (time for clearance of 98.4% of the compound) were calculated:

	10 mg/kg	30 mg/kg
Male	28 h	22 h
Female	8 h	4 h

All fat samples and female rat liver samples were below the LOQ. Tissue (liver)/plasma ratio for male rats: 10 mg/kg = 0.64; 30 mg/kg = 0.71.

V. REVIEW OF STUDIES FOR PMN SUBSTANCE 509

A. Pharmacokinetics in Rats

Groups of 3 male and 3 female rats were dosed via single oral gavage with either 10 or 30 mg/kg of PMN substance 509 (84.5%). Blood samples were taken before dosing and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after dosing. In addition fat and liver samples were taken at terminal sacrifice. Samples were analyzed for parent compound suing HPLC/MS with a level of quantitation (LOQ) of 20 ng/mL [redacted]

Clearance times for PMN substance 509 (time for clearance of 98.4% of the compound) were calculated:

	10 mg/kg	30 mg/kg
Male	12 h	22 h
Female	4 h	8 h

All fat samples and female rat plasma samples were below the LOQ. Tissue (liver)/plasma ratio for male rats: 10 mg/kg = 2.2; 30 mg/kg = 0.8.

B. *In Vitro* Metabolism

PMN substance 509 was incubated for 5, 15, 30, 45, 60, 90, or 120 minutes at 37°C with rat liver microsomes. Heat-inactivated microsomes were used as control.

After 2 hours there was no apparent loss of parent compound was noted.

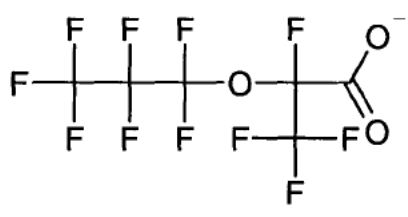
C. *In Vitro* Dermal Penetration

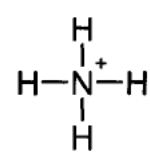
Samples of human and rat skin were dermatomed to uniform thickness of approximately 450 µm and mounted in static diffusion cells. Receptor fluid was saline. Cells were maintained at 32°C. An aqueous solution (124 mg/mL) of PMN substance 509 (86%) was added to the donor chamber and samples of the receptor fluid were removed at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours. These samples were analyzed for parent compound using HPLC/MS. A permeability coefficient (K_p in cm/h) was calculated by dividing the penetration rate at steady state (µg/cm^2/h) by the

concentration of the applied chemical (µg/cm^3).

Summary of Kinetic Parameters for 509			
		Mean	SD
Human	Lag Time (h)	1.73	1.01
	Penetration rate (µg/cm^2/h)	6.18	5.27
	K_p (cm/h)	5.02 E-05	4.3 E-05
Rat	Lag Time (h)	0.82	0.77
	Penetration rate (µg/cm^2/h)	70.3	5.27
	K_p (cm/h)	5.71 E-04	4.3 E-05

PMN Substance 08-508





PMN Substance 08-509

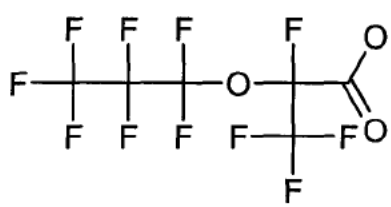


Figure 1. Structures of PMN Substances 08-508/509

REFERENCES

[redacted] 1982 (March 16 *et seq.*). [redacted]

[redacted] 2008 (Feb. 27). Determination of a permeability coefficient (K_p) for H-28308 [PMN substance 509] using human and rat skin mounted in an in vitro static diffusion cell. Conducted for DuPont. Submitted in P08-508/509.

[redacted] 2008a (Feb. 13). Biopersistence and pharmacokinetic screen in the Rat [for PMN substance 508]. Performed by DuPont Haskell Global Center for Health & Environmental Sciences for DuPont. [redacted] Submitted in P08-508/509.

[redacted] 2008b (Feb. 13). Biopersistence and pharmacokinetic screen in the Rat [for PMN substance 509]. Performed by DuPont Haskell Global Center for Health & Environmental Sciences for DuPont. [redacted]. Submitted in P08-508/509.

[redacted] 2007 (June 12). In Vitro Rat Hepatocyte Screen [for PMN substance 509]. Performed for DuPont. [redacted]. Submitted in P08-508/509.

Schanker LS, Hemberger JA. 1983. Relation between molecular weight and pulmonary absorption rate of lipid-insoluble compounds in neonatal and adult rats. Biochem. Pharmacol. 32:2599-2601.
Table 1. Pharmacokinetic Parameters for EEA in Rats.

MEMORANDUM August 22, 2008

SUBJECT: Review of Acute Oral Toxicity, Acute Dermal Toxicity, Primary Dermal Irritation, Primary Eye Irritation and Twenty Eight-Day Oral Toxicity Studies with Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)- (P08-508) or Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-, ammonium salt (1:1) (P08-509), a Two-Week Inhalation Toxicity Study with Transformation Byproducts [redacted], and Acute Oral Toxicity and Twenty Eight-Day Oral Toxicity Studies [redacted]

FROM: Larry Anderson
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TO: Steve Cragg
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Risk Assessment Division (7403)

THRU: Robert Morcock
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[redacted]

I. CONCLUSIONS

The studies reviewed below adequately meet TSCA requirements for acute oral toxicity, acute dermal toxicity, dermal irritation, and eye irritation with P08-508 or P08-509. The acute oral toxicity studies with P08-508 or P08-509 indicate low acute oral toxicity. The acute dermal toxicity study with P08-509 indicates low acute dermal toxicity. High concern for eye irritation with P09-509 is concluded. Low concern for dermal irritation with [redacted] is supported. An acute dermal toxicity study with [redacted] indicating skin irritation was not confirmed by other studies with skin treatment with [redacted] which showed low or no skin irritation. An *in vitro* test in which P08-509 was reported as corrosive is inconclusive.

A no-observable-adverse-effect level (NOAEL) was not established in 7-day oral toxicity studies with P08-508 or P08-509 in rats or mice at dose levels as low as 30 mg/kg/day based mainly on signs of liver toxicity.

In inhalation toxicity studies with 2 weeks of exposure to transformation byproducts, a NOAEL of 175,000 ppm was apparent with 1 substance and a NOAEL was not set with the other substance. In the SAT report on P08-508 and P08-509, these byproducts are noted as poor analogs.

Studies reviewed below adequately meet TSCA requirements for acute oral toxicity and 28-day oral toxicity testing with [redacted]. The acute oral LD50 is consistent with a low degree of toxicity. A no-observable-adverse-effect level (NOAEL) of 5 mg/kg/day in the 28-day oral toxicity study based on signs of kidney and liver toxicity at higher dose levels is concluded. Effects on blood were not determined in this study.

Application of the NOAEL in the study with [redacted] to P08-508 and P08-509 is not recommended, considering 30 mg/kg/day was not a NOAEL in the studies with P08-508 and P08-509 with only 7 days of treatment is not much higher than the 5 mg/kg/day NOAEL in the study with [redacted] with 28 days of treatment.

In the submission, proposed testing with P08-509 includes an inhalation LC_{50} study with histopathology in rats, a single dose pharmacokinetic study in mice, 28-day oral toxicity studies in rats and mice, an *in vitro* mouse lymphoma assay, 90-day oral toxicity studies in mice or rats, developmental toxicity studies in mice or rats, a 2-generation reproductive toxicity study in rats, a combined chronic toxicity/carcinogenicity study in rats or mice, metabolism studies in rats, and a plasma clearance study in primates. Mice or rats will be chosen based on 28-day study and metabolism study results.

II. BASIS FOR CONCLUSIONS

The PMN test substance, propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)- (P08-508) (CAS No. 13252-13-6), is a [redacted] with a molecular weight of 330, water solubility of 0.043 g/L, and vapor pressure of [redacted]. In the study reports, P08-508 is described as [redacted]

The PMN test substance, propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-, ammonium salt (1:1) (P08-509) (CAS No. 62037-80-3), is a [redacted] with a molecular weight of 347, water solubility described as dispersible, and vapor pressure of [redacted] (SAT Report). In the study reports, P08-509 is described as [redacted] (CAS No. 62037-80-3), a [redacted] which was [redacted], 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy-, ammonium salt, also called [redacted] (CAS No. 62037-80-3) or as [redacted]

[redacted]

25°C (SAT Report).

P08-508 is expected to be absorbed by all routes. Expected absorption of P08-509 is good by lung and gastrointestinal tract and poor by skin (SAT Report).

a. Acute Oral Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 425. One female Crl:CD (SD) rat per dose group were given neat test substance by gavage at a dose of 175 or 550 mg/kg, and 3 female Crl:CD (SD) rats per group were given neat test substance by gavage at a dose of 1,750 or 5,000 mg/kg. Animals were observed for survival, clinical signs, body weight, and gross pathology through sacrifice on study day 14.

No deaths occurred in the 175, 550, or 1,750 mg/kg groups. All females given 5,000 mg/kg died. by 2 days after dosing.

The reported acute oral LD_{50} was above 3,129 mg/kg.

Clinical signs in all rats included hair loss, high posture, stained and wet fur, clear ocular discharge, prostrate posture, partially closed eyes, and/or salivation. After test day 2, only hair loss was observed as a clinical sign.

Survivor body weight was normal.

Gross pathology in decedents was described as discoloration in lungs and mandible lymph nodes. Gross pathology in survivors was unremarkable.

The acute oral LD_{50} supports low acute oral toxicity in this study.

b. Acute Oral Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 401; however, the report is sketchy. What appears to be 1 male Crl-CD BR rat per dose group was given aqueous test substance solution by gavage at one of a wide range of doses from 670 to 11,000 mg/kg. Animals were observed for survival, clinical signs, and body weight through sacrifice on day 14 post-treatment.

No deaths occurred with doses at and below 3,400 mg/kg . All males given higher doses died.

The acute oral LD_{50} was above 3,,400 mg/kg. An approximate lethal dose (ALD) of 7,500 mg/kg/was reported.

Clinical signs in surviving rats included stained fur and initial weight loss. Lethargy and low posture were observed in decedents.

The acute oral LD_{50} above 5,000 mg/kg supports low acute oral toxicity in this study. Use of only 1 rat per dose group was a weakness countered by use of numerous doses and low acute oral toxicity.

c. Acute Oral Toxicity Study with [redacted]) in Rats

This study is consistent with OECD guideline 401; however, the report is sketchy. What appears to be 1 male Chr-CD rat per dose group was given aqueous test substance solution by gavage at one of a wide range of doses from 1.5 to 17,000 mg/kg. Animals were observed for survival, clinical signs, body weight, liver weight, liver histopathology, and presumably gross pathology through sacrifice on day 14 post-treatment.

No deaths occurred with doses at and below 5,000 mg/kg . All males given higher doses died. by 3.25 hours after dosing.

The acute oral LD_{50} was above 5,000 mg/kg. An ALD of 7,500 mg/kg was reported.

Clinical signs in surviving rats included discomfort, increased water intake, inactivity, polyuria, and initial weight loss in animals given 2,250, 3,400, or 5,000 mg/kg (increased liver weight and liver histopathology as enlarged hepatocytes and pronounced cell membranes were noted in these groups). Gasping and tonic convulsions were observed in decedents.

Slight to moderate degeneration in pancreas was stated, which would likely have been observed in histopathology. Because histopathology of 2 organs was reported, it is presumed that animals were examined for gross pathology and possibly histopathology of other organs with no treatment-related changes evident.

The acute oral LD_{50} above 5,000 mg/kg supports low acute oral toxicity in this study. Use of apparently only 1 rat per dose group was a weakness countered by use of numerous doses and low acute oral toxicity. Liver and pancreas were shown as potential target organs for test agent toxicity in this study.

d. Acute Dermal Toxicity Study in [redacted] in Rabbits

This study is consistent with OECD guideline 402. Onto intact skin shaved free of fur of each of 2 male New Zealand rabbits was applied 5,000 mg/kg of aqueous test material paste under semi-occlusive dressing. Exposure to test substance was 24 hours. Animals were observed for survival, clinical signs, body weight, and gross pathology through terminal sacrifice on study day 15. Irritation at test sites was scored by the Draize method. Gross pathology was not assessed.

All animals survived.

The acute dermal LD_{50} was above 5,000 mg/kg.

At test sites, erythema which reduced from severe/moderate to well-defined to very slight over time and epidermal scaling and sloughing were observed through study day 13 and were reported as cleared by study day 15. In 1 rabbit was observed necrosis attributed to test agent leaking outside the test site area and which sloughed study day 7 with alopecia evident until the end of the study. This conclusion on necrosis is uncertain to this reviewer since, if the test agent was capable of inducing this necrosis, then it seems that the test agent should have induced necrosis at the test sites. No edema at test sites was evident. This study was not a skin irritation test per guideline, i.e., OECD guideline 404; however, by Draize scoring (maximum score was 3), the test substance was moderately irritating in this study

Clinical signs and body weight were unremarkable.

Results of this study support low acute dermal toxicity by the test material.

e. Seven-Day Oral Toxicity Study with [redacted] in Rats

This study was designed to assess subacute toxicity and kinetics of the test substance given to rats for 7 days. Doses were corrected for test substance purity. In the subacute toxicity portion, 5 male and 5 female Crl:CD (SD) rats per group were given 0 (vehicle control), 30, 300, or 1,000 mg/kg/day of test substance in water by gavage daily for 7 days with terminal sacrifice on study day 8. Rats were 6 weeks old at the start of treatment. In the subacute toxicity portion, rats were evaluated for survival, clinical signs, body weight, hematology, clinical chemistry, gross pathology, histopathology, and organ weights.

All animals survived.

Clinical signs were unremarkable.

Body weight gain was slightly lower in males given 1,000 mg/kg/day.

In hematology, hemoglobin, red blood cell counts, and hematocrit were decreased in males given 300 or 1,000 mg/kg/day and in females given 1,000 mg/kg/day. In females given 1,000 mg/kg/day were increases in red blood cell distribution width, absolute reticulocyte counts, and absolute neutrophil counts.

In clinical chemistry, there were decreases in cholesterol, triglycerides, and globulin and increases in glucose in all treated groups of males, increases in biliary urea nitrogen and decreases in total protein and calcium in males given 300 or 1,000 mg/kg/day, increases in aspartate aminotransferase and alanine aminotransferase and decreases in sorbitol dehydrogenase, creatinine, and sodium in males given 1,000 mg/kg/day, increases in alanine aminotransferase and decreases in cholesterol in females given 300 or 1,000 mg/kg/day, and decreases in bilirubin, creatinine, total protein, and globulin in females given 1,000 mg/kg/day.

Absolute and relative (organ/body) liver weights were increased in all treated groups of males and in females given 1,000 mg/kg/day. Absolute and relative heart weights were decreased in males given 1,000 mg/kg/day. Absolute kidney weights were elevated in females given 1,000 mg/kg/day.

Gross pathology was unremarkable.

In histopathology, minimal to mild hepatocellular hypertrophy in liver was found in all treated groups of males and in females given 1,000 mg/kg/day.

A NOAEL is not established based on changes in clinical chemistry and organ weights indicative of liver effects in all groups of treated male rats. Hematologic data support red blood cell system toxicity and signs of anemia. Clinical chemistry and organ weight data indicate liver, kidney, and heart as target organs for test substance toxicity. Considering the multiplicity of treatment-related effects from a short treatment period of 7 days with dose levels as low as 30 mg/kg/day, the test substance toxic potential

appears high.

f. Seven-Day Oral Toxicity Study with [redacted] in Rats

This study was designed to assess subacute toxicity and kinetics of the test substance given to rats for 7 days. Doses were corrected for test substance purity. In the subacute toxicity portion, 5 male and 5 female Crl:CD (SD) rats per group were given 0 (vehicle control), 30, 100, or 300 mg/kg/day of test substance in water by gavage daily for 7 days with terminal sacrifice on study day 8. Rats were 6 weeks old at the start of treatment. In the subacute toxicity portion,
rats were evaluated for survival, clinical signs, body weight, hematology, clinical chemistry, gross pathology, histopathology, and organ weights.

All animals survived.

Clinical signs were unremarkable.

Body weight gain was normal.

In hematology, hemoglobin and hematocrit were decreased in males given 300 mg/kg/day and red blood cell counts were lower in females given 300 mg/kg/day,

In clinical chemistry, there were decreases in cholesterol and increases in alkaline phosphatase in all treated groups of males, decreases in globulin and triglycerides in males given 100 or 300 mg/kg/day, increases in biliary urea nitrogen and glucose and decreases in creatinine, total protein, and calcium in males given 300 mg/kg/day, and decreases in bilirubin in females given 300 mg/kg/day.

Absolute and relative (organ/body) liver weights were increased in all treated groups of males and in females given 300 mg/kg/day. Relative kidney weights were elevated in all treated groups of males, and absolute kidney weights were higher in males given 100 mg/kg/day.

Gross pathology was unremarkable.

In histopathology, minimal to mild hepatocellular hypertrophy in liver was found in all treated groups of males and females.

A NOAEL is not established based on changes in clinical chemistry and organ weights indicative of liver effects in all groups of treated male rats. Hematologic data in rats given 300 mg/kg/day support red blood cell system toxicity and signs of anemia. Clinical chemistry and organ weight data indicate liver and kidney as target organs for test substance toxicity. Considering the multiplicity of treatment-related effects from a short treatment period of 7 days with dose levels as low as 30 mg/kg/day, the test substance toxic potential appears high.

g. Seven-Day Oral Toxicity Study with [redacted] in Mice

This study was designed to assess subacute toxicity and kinetics of the test substance given to mice for 7 days. Doses were corrected for test substance purity. In the subacute toxicity portion, 5 male Crl:CD1 (ICR) mice per group were given 0 (vehicle control) or 30 mg/kg/day of test substance in water

by gavage daily for 7 days with terminal sacrifice on study day 8. Mice were 6 weeks old at the start of treatment. In the subacute toxicity portion, rats were evaluated for survival, clinical signs, body weight, gross pathology, histopathology, and organ weights.

All animals survived.

Clinical signs were unremarkable.

Body weight gain was slightly higher in treated males.

Absolute and relative (organ/body) liver weights were increased in treated males.

Gross pathology was unremarkable.

In histopathology, minimal single cell necrosis of hepatocytes, moderate hepatocellular hypertrophy, and moderate increases in mitotic figures, all in liver, was found in treated males.

A NOAEL is not established based on signs of liver toxicity. Considering the treatment-related toxic signs in liver from a short treatment period of 7 days with a dose level as low as 30 mg/kg/day, the test substance toxic potential appears strong.

h. Seven-Day Oral Toxicity Study with [redacted] in Mice

This study was designed to assess subacute toxicity of the test substance given to mice for 7 days. Doses were corrected for test substance purity. In the subacute toxicity portion, 5 male Crl:CD1 (ICR) mice per group were given 0 (vehicle control) or 30 mg/kg/day of test substance in water by gavage daily for 7 days with terminal sacrifice on study day 8. Mice were 6 weeks old at the start of treatment. In the subacute toxicity portion, rats were evaluated for survival, clinical signs, body weight, gross pathology, histopathology, and organ weights.

All animals survived.

Clinical signs were unremarkable.

Body weight gain was slightly higher in treated males.

Absolute and relative (organ/body) liver weights were increased in treated males.

Gross pathology was unremarkable.

In histopathology, minimal single cell necrosis of hepatocytes, moderate hepatocellular hypertrophy, and moderate increases in mitotic figures, all in liver, was found in treated males.

A NOAEL is not established based on signs of liver toxicity. Considering the treatment-related toxic signs in liver from a short treatment period of 7 days with a dose level as low as 30 mg/kg/day, the test substance toxic potential appears strong. In both 7-day studies in mice described herein, the results were similar.

I. Acute Dermal Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 402. Onto intact skin shaved free of fur of each of 5 male and 5 female Crl:CD (SD) rats was applied 5,000 mg/kg of neat test material under semi-occlusive dressing. Exposure to test substance was 24 hours. Animals were observed for survival, clinical signs, body weight, and gross pathology through terminal sacrifice on study day 15. Irritation at test sites was scored by the Draize method.

All animals survived.

The acute dermal LD_{50} was above 5,000 mg/kg.

There were no signs of irritation at application sites in males (Draize score of 0). At application sites in females, there were well-defined erythema (maximum Draize score of 2) which disappeared by 2 days post-treatment, no evidence of edema, and hyperkeratosis and ulceration which cleared by day 13 after treatment. This study was not a skin irritation test per guideline, i.e., OECD guideline 404; however, by Draize scoring, the test substance was slightly irritating in females in this study

Clinical signs, gross pathology, and body weight were unremarkable.

Results of this study support low acute dermal toxicity by the test material.

j. Eye Irritation Study with [redacted] in Rabbits

This study is consistent with OECD guideline 405. Into one eye of 1 male New Zealand white rabbits was applied 0.1 ml of undiluted test material. Irritation was scored according to the Draize method and examined with fluorescein stain during 28 hours post-treatment.

Discoloration of the conjunctival membrane of the treated eye was interpreted as necrosis. Corneal opacity, iritis, and chemosis and discharge in conjunctivae were observed. Observed eye effects did not reverse, and the animal was killed at the end of the observation for humane reasons. The maximum Draize score was 61, in the criteria for "severely irritating", but the required observation period of 7 days was not done to see if the criteria for stronger severity would have been met.

The investigators concluded eye effects "...appeared to look like necrosis". Considering results of this study as signs of necrosis, a high concern for eye irritation by the test material is concluded..

k. Dermal Irritation Study with [redacted] in Rabbits

This study is consistent with OECD guideline 404. Onto intact skin clipped free of fur of each of 3 New Zealand white rabbits (sex not reported) was applied 0.5 ml of undiluted test material under semi-occlusive dressing. Exposure to test substance was 4 hours. Irritation was scored according to the Draize method during 72 hours post-treatment.

Very slight to well-defined erythema observed on test sites of all rabbits cleared by 24 hours post-treatment. No signs of edema were found. The maximum mean Draize score was 1.9 at 60 minutes after treatment.

By Draize criteria, the test material was slightly irritating to skin only at the 60-minute observation time, which supports low concern for this effect.

l. Acute Oral Toxicity Study with [redacted] in Mice

This study is consistent with OECD guideline 425. Female Crl:CD (ICR) mice were given test substance suspended in deionized water by gavage at a dose of 175 (1 mouse), 550 (3 mice) , or 1,750 mg/kg (3 mice). Animals were observed for survival, clinical signs, body weight, and gross pathology through sacrifice on study day 14.

No deaths occurred in the 175 and 550 mg/kg groups. All females given 1,750 mg/kg died on the day of or the day after dosing.

The estimated acute oral LD_{50} was 1,030 mg/kg.

Clinical signs in decedents were lethargy and low posture. No clinical signs were observed in survivors.

Survivor body weight was normal.

Gross pathology was unremarkable.

The estimated acute oral LD_{50} of 1,030 mg/kg supports low acute oral toxicity in this study.

m. Acute Oral Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 425. Female Crl:CD (SD) rats were given neat test substance by gavage at a dose of 175 (2 rats), 550 (4 rats) , or 1,750 mg/kg (3 rats). Animals were observed for survival, clinical signs, body weight, gross pathology, and histopathology of gross lesions, heart, liver, and kidneys through sacrifice on study day 14-17.

No deaths occurred in the 175 mg/kg group. Two females given 550 mg/kg died on study day 2 or study day 17 (killed *in extremis*), and all females given 1,750 mg/kg died on the day of or the day after dosing. Cause of death was diagnosed as acute gastritis.

The estimated acute oral LD_{50} was 550 mg/kg.

Clinical signs in rats given 1,750 mg/kg included oral discharge, closed eyes, lethargy, wet fur, high posture, and ataxia. Clinical signs in rats given 550 mg/kg included lung noise, oral discharge, no feces, high posture, wet and stained fur No clinical signs other than stained and wet fur were observed in rats given 175 mg/kg.

Survivor body weight was normal. One rat given 550 mg/kg and sacrificed *in extremis* on day 17 lost weight.

Gross pathology was unremarkable except for discoloration, increased thickness, and/or ulcers/erosions in stomach of decedents.

Histopathology was normal except for degenerative necrosis, erosion/ulcer, and edema in stomach of decedents and acute tubular necrosis in kidney of decedents..

The estimated acute oral LD_{50} of 550 mg/kg supports low acute oral toxicity in this study. Irritation toxicity in stomach, the site of direct exposure, and kidney toxicity were evident at doses above 175 mg/kg.

n. Acute Oral Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 425. Male Crl:CD (SD) rats were given neat test substance by gavage at a dose of 175 (1 rat), 550 (2 rats) , 1,750 (4 rats), or 5,000 mg/kg (3 rats). Animals were observed for survival, clinical signs, body weight, and gross pathology through sacrifice on study day 14.

No deaths occurred in the 175 and 550 mg/kg groups. One male given 1,750 mg/kg died on study day 2, and all males given 5,000 mg/kg died on study day 1 or 2.

The estimated acute oral LD_{50} was 1,750 mg/kg.

Clinical signs in survivors included lethargy, wet and stained fur, and low posture. Clinical signs in decedents included lethargy, lung noise, decreased muscle tone, and stained and wet fur.

Survivor body weight was normal.

Gross pathology was unremarkable except for stained skin, expanded lungs, eye discoloration, and stomach discoloration in decedents.

The estimated acute oral LD_{50} of 1,750 mg/kg supports low acute oral toxicity in this study.

o. Corrositex *In Vitro* Test with [redacted]

Corrositex is described as a standardized and quantitative *in vitro* corrosivity test. However, this test does not presently meet OPPTS and OECD guidelines for skin irritation testing. Basically, the ability of the presumed corrosive test substance to penetrate a collagen biomembrane, as determined by color change in a liquid chemical detection medium, is compared to positive and negative controls. The investigators concluded that since the test substance penetrated the barrier as did the positive control (sulfuric acid), the test substance should be considered corrosive, However, it took around 1 hour and 8 minutes for the test substance to penetrate, whereas the positive control penetrated in approximately 1 minute. If time of penetration is a determining factor in this test, the results supporting the test agent as corrosive seem weak. To assess the skin irritation potential of the test substance, testing per OECD guideline 404 is recommended.

p. Two-Week Inhalation Toxicity Study with Transformation Byproducts in Rats

This study was done to assess systemic inhalation toxicity and the presence of micronuclei in bone marrow. Micronuclei assessment is done in a separate OPPT/RAD review. Ten male Crl:CD BR rats per dose group were exposed by inhalation to target concentrations of 0 (air control), 5,000, 25,000,

or 175,000 ppm[redacted] or to 25,000 ppm[redacted] an analytical concentration (measured by gas chromatography) of 0 (air control), 750, or 2,199 ppm. 6 hours/day, 5 days/week for 2 weeks. Five rats/group were sacrificed at the end of exposure, and 5 rats/group were sacrificed at the end of a 2-week recovery period. Nominal concentrations were 0, 750, and 3,000 ppm. Exposure was whole-body. Temperature and humidity in the inhalation chamber apparently were satisfactory. During exposure, oxygen was added as needed to maintain an oxygen level of at least 19 %. Rats were 7 weeks old at the start of the study. Animals were observed for survival, clinical signs, body weight, hematology, clinical chemistry, urinalysis, organ weights, histopathology, and gross pathology.

All animals survived.

Body weight was normal.

Clinical signs were unremarkable except for reduced activity during exposure to 175,000 ppm with recovery after cessation of exposure.

Hematology, clinical chemistry, and urinalysis were normal.

Mean absolute brain weights were increased in animals exposed to 5,000, 25,000, or 175,000 ppm of [redacted] However, relative (organ/body) brain weights were unaffected.

Mean absolute and relative liver weights were elevated in rats exposed to [redacted]

Gross pathology was unremarkable.

Except for hyaline droplets in kidney in animals exposed to 175,000 ppm, there were no treatment-related histopathologic findings.

A NOAEL of 175,000 ppm with [redacted] is concluded in this study. Hyaline droplets in kidney in animals exposed to 175,000 ppm are a sign of kidney nephropathy in male rats exposed to hydrocarbons which EPA has stated as irrelevant to humans. Increased absolute and relative liver weights preclude conclusion of 25,000 ppm as a NOAEL with [redacted].

Recognizing no female rats on study, only 1 exposure level of [redacted], and only 2 weeks of exposure, this study is patterned after OECD guideline 412.. Whole-body exposure is permissible per guideline. Since the exposure atmosphere was described as vapor, there apparently was no detectable test substance aerosol in the atmosphere at the high levels used.

q. Acute Oral Toxicity Study [redacted] in Rats

This study is consistent with OECD guideline 423. Three female Crl:CD (SD) IGS BR rats were given 2,000 mg/kg and 6 female rats were given 300 mg/kg of test substance in distilled water. Dosing was by gavage. Animals were sacrificed on day 14 post-treatment and were observed for survival, clinical signs, body weight, and gross pathology.

No deaths occurred with 300 mg/kg. All animals given 2,000 mg/kg died within 1 day of treatment. The acute oral LD_{50} was between 300 and 2,000 mg/kg.

Clinical signs in decedents included hunched posture, lethargy, ataxia, decreased and noisy respiration, diuresis, and dehydration. Survivors showed no clinical signs. Body weight was normal in survivors.

Gross pathology was unremarkable in survivors. In decedents were found abnormally red lungs, dark liver, and dark kidneys.

Because 300 mg/kg, which did not cause death, is close to 500 mg/kg, which is the lowest dose in the OPPT criteria for low acute oral toxicity, and 2,000 mg/kg is well above 500 mg/kg, low acute oral toxicity is concluded to be supported in this study.

r. Twenty Eight-Day Oral Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 407, and dose levels were based on a 14-day oral dose toxicity study. Five male and 5 female Crl:CD (SD) rats per group were given 0 (vehicle control), 5, 25, or 100 mg/kg/day of test substance in purified water by gavage daily for 28 days with terminal sacrifice on day 29. Additional groups of 5 males and 5 females per group were similarly treated with 0 (vehicle controls) or 100 mg/kg/day and sacrificed after 14 days of recovery. Rats were 5 weeks old at the start of the study. The rats were evaluated for survival, functional observational battery, motor activity, clinical signs, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology.

All animals survived.

In hematology, prothrombin time and reticulocytes were increased in males and females given 100 mg/kg/day, respectively.

In clinical chemistry, alanine aminotransferase (ALT) and albumin/globulin ratio were increased in males given 100 mg/kg/day, ALT was increased in treated recovery males, cholesterol was decreased in males given 100 mg/kg/day, and bilirubin was decreased in females given 100 mg/kg/day.

Absolute and relative (organ/body) kidney weights were increased in males given 25 or 100 mg/kg/day and in treated recovery females, absolute and relative liver weights were increased in males given 100 mg/kg/day, and relative adrenal weights were increased in males given 100 mg/kg/day.

In gross pathology, there were elevations of the limiting ridge of the forestomach in 4 males and 1 female given 100 mg/kg/day and enlarged liver in 2 males given 100 mg/kg/day.

In histopathology, there were squamous cell hyperplasia in the limiting ridge of the forestomach in both sexes given 100 mg/kg/day, diffuse hypertrophy of hepatocytes with granular-degeneration in liver of males given 100 mg/kg/day, focal necrosis of hepatocytes in liver in 1 female given 100 mg/kg/day, tubular cell epithelium hyperplasia in kidney in 1 female given 100 mg/kg/day, and a solitary cyst in kidney medulla in 1 male given 100 mg/kg/day.

Other findings were unremarkable.

Based on increases in absolute and relative kidney weights in males at higher dose levels, the investigators concluded a NOEL of 5 mg/kg/day. This conclusion is acceptable as a NOAEL. In clinical chemistry and pathology, signs of kidney, liver, and forestomach toxicity were found in animals given 100 mg/kg/day.

MEMORANDUM September 24, 2008

SUBJECT: Review of Twenty Eight-Day Oral Toxicity Studies with 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-, ammonium salt (1:1) in Rats and Mice (P08-509)

FROM: Larry Anderson
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TO: Steven Cragg
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THRU: Robert Morcock
Chief
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[redacted]

I. CONCLUSIONS

The studies reviewed below adequately meet TSCA requirements for 28-day oral toxicity testing with P08-509. No-observable-adverse-effect levels (NOAELs) of 0.3 mg/kg/day in rats based on signs of anemia and liver and kidney effects at higher dose levels and 0.1 mg/kg/day in mice based on signs of anemia and liver effects at higher dose levels. Additional signs of toxicity at the top dose levels were observed in these studies. Although the NOAELs are similar and unless otherwise justified, the NOAEL in mice is proposed as operational since overall results in these studies favor mice as the more sensitive species for P08-509 toxicity.

Comment on relevance of data indicative of peroxisome proliferation activity to cancer in these studies is deferred to carcinogenesis specialists in OPPT/RAD.

Opinion on potential relationship of lower globulin levels in clinical chemistry to antibodies in these studies by OPPT/RAD immunologists is recommended.

In an earlier submission on this case, proposed testing with P08-509 included an inhalation LC_{50} study with histopathology in rats, a single dose pharmacokinetic study in mice, 28-day oral toxicity studies in rats and mice (these studies are reviewed herein), an *in vitro* mouse lymphoma assay, 90-day oral toxicity studies in mice or rats, developmental toxicity studies in mice or rats, a 2-generation reproductive toxicity study in rats, a combined chronic toxicity/carcinogenicity study in rats or mice, metabolism studies in rats, and a plasma clearance study in primates. Mice or rats will be chosen based on 28-day study and metabolism study results.

II. BASIS FOR CONCLUSIONS

The PMN test substance, propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-, ammonium salt (1:1) (P08-509) (CAS No. 62037-80-3), is [redacted] with a molecular weight of 347, water solubility described as dispersible, and vapor pressure [redacted] (SAT Report). In the study reports, P08-509 is described as [redacted] (CAS No. 62037-80-3), a [redacted] which was [redacted]

Expected absorption of P08-509 is good by lung and gastrointestinal tract and poor by skin (SAT Report).

a. Twenty Eight-Day Oral Toxicity Study in Rats

This study is consistent with OECD guideline 407, and dose levels were based existing toxicity studies. Ten male Crl:CD(SD) rats per group were given 0 (vehicle control), 0.3, 3, or 30 mg/kg/day of test substance in deionized water by gavage daily for 28 days with terminal sacrifice on day 29. Ten female Crl:CD(SD) rats per group were given 0 (vehicle control), 3, 30, or 300 mg/kg/day of test substance in deionized water by gavage daily for 28 days with terminal sacrifice on day 29. Ten male and 10 female Crl:CD(SD) male rats per group were similarly treated with 0 (vehicle control), 30 (males), or 300 (females) mg/kg/day and killed after 29 days of recovery following treatment. Rats were 7 weeks old at the start of treatment. Rats were evaluated for survival, clinical signs, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, histopathology, and cytochrome P450 content and beta-oxidation activity in liver.

All animals survived.

Clinical signs were noted as occasional yellow staining of the urogenital area in females given 300 mg/kg/day.

In hematology, decreases in red blood cell counts, hemoglobin, and hematocrit and increases in absolute reticulocyte counts in males given 3 or 30 mg/kg/day were reported.. These data are:

	Dose Group (mg/kg/day)			
Data (Mean ± S.E.)	0	0.3	3	30
Red blood cells (mil/μL)	8.44 ± 0.094	8.27 ± 0.104	8.12* ± 0.065	7.97** ± 0.080
Hemoglobin (g/dL)	16.3 ± 0.11	16.3 ± 0.15	15.8* ± 0.13	15.2** ± 0.19
Hematocrit (%)	45.6 ± 0.53	44.9 ± 0.43	43.4** ± 0.44	42.0** ± 0.51

Absolute reticulocytes (thousands/μL)	188.9 ± 11.77	189.9 ± 11.09	196.1 ± 10.99	224.9 ± 7.65

* $p < 0.05$ ** $p < 0.01$

In clinical chemistry, there were higher albumin/globulin ratios and lower globulin levels in males given 3 or 30 mg/kg/day, elevated glucose, urea nitrogen and albumin levels in males given 30 mg/kg/day, lower triglyceride and cholesterol levels (without dose relationship) in males given 0.3, 3, or 30 mg/kg/day, and higher albumin/globulin ratios and lower globulin levels in females given 300 mg/kg/day.

There were increases in absolute and relative (organ/body) liver weights in males given 3 or 30 mg/kg/day and in females given 300 mg/kg/day and increases in absolute and relative kidney weights in males given 3 or 30 mg/kg/day. These increases were dose-related.

Histopathologic findings in liver included minimal or mild hepatocellular hypertrophy in 4 males given 3 mg/kg/day, 7 males given 30 mg/kg/day, and 4 females given 300 mg/kg/day, minimal hepatocellular necrosis in 3 males given 30 mg/kg/day (also found as minimal or mild in 1 female in each group given 0, 30, or 300 mg/kg/day), and mild single cell necrosis in 1 of the males with hepatocellular necrosis given 30 mg/kg/day.

Increased beta-oxidation activity in liver of males given 0.3, 3, or 30 mg/kg/day and females given 30 or 300 mg/kg/day was reported. Cytochrome P450 content was elevated in males given 30 mg/kg/day.

Other findings were unremarkable.

The investigators concluded 30 mg/kg/day in males and 300 mg/kg/day in females as NOAELs, dismissing all changes in treated groups as within historical control ranges at the testing facility and as adaptive responses.

This reviewer concludes 0.3 mg/kg/day as a NOAEL in males based on dose-related trends and statistical significance of change in hematologic findings in the above table as signs of anemia (red blood cell counts, hematocrit, and hemoglobin were also decreased in male Crl:CD(SD) rats given 300 or 1,000 mg/kg/day of test substance for 7 days in a toxicity study discussed in a separate OPPT/RAD review for P08-508/509), increases in weights of 2 organs, liver and kidney, in higher dose groups as signs of sensitivity to treatment with test substance, and pathology as hepatocellular hypertrophy in liver limited to males in the 2 higher dose groups. Hepatocellular necrosis in males given 30 mg/kg/day is considered of importance because this finding was in multiple animals and was not in other dose groups of males. This finding is females, although found in a control as well as in treated animals, was not dose-related with only 1 animal per group where found and was not dose-related in severity.(mild in control, minimal in each of treated). Lower triglyceride and cholesterol levels in clinical chemistry in all treated groups of males is questioned as an effect because these levels were similar with no dose relationship across groups. Concern for hematologic effects in this study is also based on similar findings in a second species, mouse, as described below.

This reviewer concludes 30 mg/kg/day as a NOAEL in females based on increased liver weights and liver pathology as hepatocellular hypertrophy in females given 300 mg/kg/day.

Assessment of increases in beta-oxidation activity and cytochrome P450 content as relevant to peroxisome proliferation as a marker for carcinogenesis in treated groups is deferred to OPPT/RAD specialists in carcinogenesis.

Assessment of impact of lower globulin levels in serum chemistry on antibodies by OPPT/RAD immunologists is recommended.

b. Twenty Eight-Day Oral Toxicity Study in Mice

This study is consistent with OECD guideline 407, and dose levels were based existing toxicity studies. Ten male and 10 female Crl:CD-1 mice per group were given 0 (vehicle control), 0.1, 3, or 30 mg/kg/day of test substance in deionized water by gavage daily for 28 days with terminal sacrifice on day 29. Ten male and 10 female Crl:CD-1 mice per group were similarly treated with 0 (vehicle control), 30 (males), or 300 (females) mg/kg/day and killed after 28 days of recovery following treatment. Mice were 7 weeks old at the start of treatment. Mice were evaluated for survival, clinical signs, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, histopathology, and cytochrome P450 content and beta-oxidation activity in liver.

All animals survived except 1 control female and 1 female given 30 mg/kg/day (this death was not attributed to treatment).

Clinical signs were unremarkable.

Body weight gain and food consumption were higher in both sexes during treatment with 30 mg/kg/day.

In hematology, decreases in red blood cell counts, hemoglobin, and hematocrit in males given 3 or 30 mg/kg/day were reported.. These data are:

	Dose Group (mg/kg/day)			
Data (Mean ± S.E.)	0	0.1	3	30
Red blood cells (mil/μL)	8.80 ± 0.173	8.44 ± 0.149	8.28 ± 0.142	8.13* ± 0.149
Hemoglobin (g/dL)	14.1 ± 0.18	13.8 ± 0.16	13.4* ± 0.16	13.1** ± 0.18
Hematocrit (%)	40.1 ± 0.57	38.8 ± 0.38	38.1* ± 0.48	37.5** ± 0.51

* $p < 0.05$ **$p < 0.01$

Monocytes were higher in males given 30 mg/kg/day. White cell counts, platelet counts, and absolute lymphocytes were elevated and mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were lower in treated recovery males

In clinical chemistry, there were higher sorbitol dehydrogenase, alkaline phosphatase, albumin/globulin ratios and lower globulin levels in males given 3 or 30 mg/kg/day, elevated alanine aminotransferase, aspartate aminotransferase, urea nitrogen, total protein, and albumin levels in males given 30 mg/kg/day, lower cholesterol levels (without dose relationship) in males given 0.1, 3, or 30 mg/kg/day, higher sorbitol dehydrogenase in treated recovery males, greater sorbitol dehydrogenase, alkaline phosphatase, and albumin levels in females given 30 mg/kg/day, and higher albumin/globulin ratios and lower globulin levels in females given 3 or 30 mg/kg/day.

There were increases in absolute and relative (organ/body) liver weights in both sexes given 3 or 30 mg/kg/day and in treated recovery males, decreases in absolute and relative uterine weights in females given 30 mg/kg/day, increases in absolute and relative adrenal weights in males given 30 mg/kg/day, increases in absolute liver and adrenal weights in treated recovery females, and increases in absolute and relative kidney weights in females given 0.1 or 30 mg/kg/day. Liver weight increases were dose-related.

In gross pathology, there were enlarged livers in males given 30 mg/kg/day.

Histopathologic findings in liver included mild or moderate hepatocellular hypertrophy in liver in all males and females given 3 or 30 mg/kg/day, increased mitosis in liver in both sexes given 30 mg/kg/day, minimal or mild hepatocellular necrosis in liver in 1 male given 3 mg/kg/day and 1 male given 30 mg/kg/day, minimal single cell necrosis in liver in males given 3 mg/kg/day and in both sexes given 30 mg/kg/day, minimal hypertrophy in adrenal cortex in males given 30 mg/kg/day, minimal hyperplasia in glandular stomach in 1 male given 30 mg/kg/day, minimal tubular necrosis in kidney and severe necrosis in testes in 1 treated recovery male, and minimal hepatocellular necrosis in liver in 1 control recovery male, 1 treated recovery male, and 2 treated recovery females .

Increased beta-oxidation activity in liver of males given 0.1, 3, or 30 mg/kg/day and females given 3 or 30 mg/kg/day was reported. Cytochrome P450 content was decreased in males given 3 or 30 mg/kg/day and in treated recovery males.

Other findings were unremarkable.

The investigators concluded 0.1 mg/kg/day in males and 3 mg/kg/day in females as NOAELs based on single cell necrosis of liver hepatocytes and increases in liver enzymes at higher dose levels.

This reviewer concludes 0.1 mg/kg/day as a NOAEL in both sexes based on liver abnormalities indicated by overall data pertinent to this organ, i.e., changes in various levels of enzymes and proteins relevant to liver in clinical chemistry, increases in liver weights, and various signs of liver pathology in animals in the higher dose groups. Additional support for this NOAEL is males is various dose-related trends and statistical significance of change in hematologic findings in the above table as signs of anemia. Lower cholesterol levels in clinical chemistry in all treated groups of males is questioned as an effect because these levels were similar with no dose relationship across groups. Increased organ weights and abnormal pathology support the adrenal as a target organ in males given 30 mg/kg/day. Decreased uterine weights suggest sensitivity of this organ to treatment in the 30 mg/kg/day group. Kidney weight data in treated female groups suggest an effect in the 30 mg/kg/day group, but concluding an effect in the 0.1 mg/kg/day group is relatively uncertain considering kidney weights in the 3 mg/kg/day group were actually lower.

Assessment of increases in beta-oxidation activity and cytochrome P450 content as relevant to peroxisome proliferation as a marker for carcinogenesis in treated groups is deferred to OPPT/RAD specialists in carcinogenesis.

Assessment of impact of lower globulin levels in serum chemistry on antibodies by OPPT/RAD immunologists is recommended.

09/03/08
MEMORANDUM

SUBJECT: P08-508/509: Immunotoxicity Standard Review

FROM: Ronald E. Ward Ph.D., Microbiologist/Immunologist
RAD/SSB (7403M)

THRU: Donald Rodier, Branch Chief
RAD/SSB (7403M)

TO: Steven Cragg Ph.D., Technical Integrator
NCSAB (7403M)

[redacted]

Conclusion: Based on analog data, PMN 08-508 (2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoic acid) and P08-509 (2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoic acid ammonium salt) would have the potential to be an immunotoxicity hazard. In addition, PMN 08-508-508 would be a skin sensitization hazard.

Basis for Conclusion:

There were two dermal sensitization tests (Local Lymph Node Assays (LLNA)) sent with this PMN submission (1). PMN 08-508 tested positive in a mouse LLNA, while PMN 08-509 tested negative. Thus PMN 08-508 would be a skin sensitization hazard.

There were no other direct immunotoxicity test data associated with this PMN. The following conclusions reached here are based on analog test data.

There is a concern for immunotoxicity based on PFOA (perfluorooctanoic acid) as analog. Based on published studies, PFOA is immunotoxic in mice (2,3,4,5). Feeding C57Bl/6 mice a diet containing 0.02% PFOA resulted in adverse effects to both the thymus and spleen. In addition, this feeding regimen resulted in suppression of the specific humoral immune response to horse red blood cells, and suppression of splenic lymphocyte proliferation in response to LPS and ConA. The suppressed mice recovered their ability to generate a humoral immune response when they were fed a diet devoid of PFOA. Studies using transgenic mice showed that the peroxisome proliferator-activated receptor alpha was involved in causing the adverse effects to the immune system.

In a May 2008 publication, DeWitt et al. (6) examined PFOA effects on humoral and cellular immunity using standard assays for assessing immune function, and also derived dose–response data. To perform the dose response experiment, groups of C57BL/6N female mice (8 animals per dose group) were given PFOA in drinking water for 15 days. The resulting PFOA doses were 30, 15, 7.5, 3.75, 1.88 and 0.94 mg/kg/day, based on average daily water consumption rates. Mice were immunized with sheep red blood cells in Freund's complete adjuvant on day 11 of exposure; immune responses were determined 1 day post-exposure.

The results showed that SRBC-specific IgM synthesis (ELISA titers) was suppressed at exposures $\geq$ 3.75 mg PFOA/kg/day in a dose-dependent manner. A NOAEL for suppressed IgM production was identified as1.88 mg PFOA/kg/day and a LOAEL for suppressed IgM production was 3.75 mg PFOA/kg/day. The conclusion of these experiments was that IgM antibodies were suppressed after PFOA exposure.

Based on the studies detailed above, P08-508/509 would have the potential to be an immunotoxicity hazard. In addition, PMN 08-508-508 would be a skin sensitization hazard.

Testing Suggestion

If needed, direct immunotoxicity testing (OPPTS 870.7800) could be used to support the conclusion.

References

1. P08-508/509 SAT report (2008).
2.Yang, Q., Xie, Y., and Depierre, W. 2000. Effects of peroxisome proliferators in the thymus of spleen and mice. Clin. Exp. Immunol. 122:219-226.
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4. Yang, Q., Xie, Y., Alexson, S.E.H., Nelson, B.D., and DePierre, J. W. 2002a. Involvement of the peroxisome proliferator-activated receptor alpha in the immunomodulation caused by peroxisome proliferators in mice. Biochem. Pharmacol. 63: 1893-1900.
5. Yang, Q., Abedi-Valugerdi, M., Xie, Y. Zhao, X., Moller, G., Nelson, B.D., and DePierre, J. W. 2002b. Potent suppression of the adaptive immune response in mice upon dietary exposure to the potent peroxisome proliferator, perfluorooctanoic acid. International Immunopharmacology 2, 389-397.
6.DeWitt, J. C, et al. 2008. Perfluorooctanoic Acid-Induced Immunomodulation in Adult C57BL/6J or C57BL/6N Female Mice. Environmental Health Perspectives 116:644-650.

August 29, 2008

MEMORANDUM

SUBJECT: Mutagenicity Hazard Review of P08-508 and -509

FROM: Michael C. Cimino, Ph.D.
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TO: Steven Cragg, PhD, DABT
Technical Integrator
Existing Chemical Assessment Branch

THRU: Donald Rodier
Branch Chief
Science Support Branch
Risk Assessment Division (7403M)

[redacted]

I. CONCLUSION

Based on data on the PMNs themselves and on analogues, P08-508 and P08-509 are or may be: (a) not gene mutagens in two species of prokaryotes; (b) chromosome mutagens in mammalian and human cells in culture, but not in mammals *in vivo* and; (c) not inducers of DNA effects in mammalian cells *in vivo*.

The positive data on the PMN for *in vitro* chromosomal aberrations in mammalian and human cells are of some concern. However, the negative responses for *in vivo* chromosomal effects as micronuclei and as chromosomal aberrations, and for induction of DNA effects, alleviate that concern. There is no basis for recommending additional mutagenicity testing for the PMNs, and there is little support for a cancer concern based upon mutagenicity. The lack of mutagenicity concern does not negate a cancer concern should such concern be based upon nongenotoxic information.

II. STRUCTURES OF P08-508, -509 AND ANALOGUES

Not imported

III. BASIS FOR THE CONCLUSIONS

Mutagenicity data were provided with the Premanufacturing Notice on P08-508 and -509:

A) P08-508 is Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-; [redacted] CAS# 13252-13-6
B) P08-509 is Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-, ammonium salt (1:1); [redacted] CAS# 62037-80-3

and on three transformation products:

[redacted]yl [redacted]

The structures of these chemicals are provided in Section II (not imported). The data are reviewed below.

A) P08-508

I. Bacterial reverse mutation

P08-508 was tested in a bacterial reverse mutation assay, as reported in "[redacted] Bacterial reverse mutation test", conducted by [redacted] (Report Revision 1) dated February 22, 2008 (PMN Attachment 79). The PMN [redacted]) was tested in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and in *Escherichia coli* strain WP2*uvrA*, both without and with metabolic activation using Aroclor 1254-induced rat liver S9. It was tested at eight dose levels ranging from 33.3 to 5,000 µg/plate, in duplicate plates per dose level. Dose selection was acceptable for a noncytotoxic chemical. An independent repeat was conducted, in triplicate plates, at five dose levels from 333 to 5,000 µg/plate. The chemical did not induce significant increases in gene mutations under any test condition. Concurrent negative (the solvent, sterile water) and positive controls produced appropriate responses.

II. *In vitro* chromosome aberration

The PMN also was tested in an *in vitro* mammalian chromosome aberration assay, as reported in "[redacted] *In vitro* mammalian chromosomal aberration test in Chinese hamster ovary cells," also conducted by [redacted] (Report Revision 1) dated February 25, 2008 (PMN Attachment 78). The PMN (purity as above) was tested both without and with metabolic activation using rat liver S9, as above. Dose selection was based upon the results of a Preliminary Toxicity Assay. The dose level of 3471 µg/ml, which represented 10mM, was the limit dose for this chemical in this assay. Two experiments were conducted, in duplicate flasks for each treatment group. The first experiment involved exposure of the cells for four hours with 16h recovery, conducted without and with activation. Five dose levels of 100, 500, 1,000, 2,000 and 3,471 µg/ml were applied. The highest three doses were used for mutagenicity evaluation. The second experiment involved exposure for 20h with no recovery period, and was conducted without activation only. The same five dose levels were applied as for the first experiment. Cytotoxicity (>50%) was noted only at the highest dose in the 20hr treatment. Thus the three highest surviving doses used for mutagenicity evaluation in the second experiment were 100, 500 and 1,000 µg/ml. Dose selection was acceptable. No significant increases in structural aberrations were detected under any treatment condition. Numerical aberrations (polyploidy) were increased in a statistically-significant manner, with dose responses, in the first (4h) experiment both without and with activation. Concurrent negative (sterile water) and positive controls (mitomycin C and cyclophosphamide for non-activated and activated assays, respectively) produced appropriate responses.

In summary, P08-508 is not a gene mutagen in two species of prokaryotes both without and with activation. It induces chromosomal mutations in mammalian cells *in vitro* in the form of numerical but not structural aberrations both without and with activation.

B) P08-509

I. Bacterial reverse mutation

P08-509 was tested in a bacterial reverse mutation assay, as reported in "[redacted] Bacterial reverse mutation test", conducted by [redacted], study dated July 26, 2007 (PMN Attachment 68). The PMN ([redacted]) was tested in *Salmonella typhimurium* strains [redacted] and in *Escherichia coli* strain WP2*uvrA*, both without and with metabolic activation using Aroclor 1254-induced rat liver S9. It was tested at eight dose levels ranging from 33.3 to 5,000 µg/plate, in duplicate plates per dose level. Dose selection was acceptable for a noncytotoxic chemical. An independent repeat was conducted, in triplicate plates, at five dose levels from 333 to 5,000 µg/plate. The chemical did not induce significant increases in gene mutations under any test condition. Concurrent negative (the solvent, sterile water) and positive controls produced appropriate responses.

II. *In vitro* chromosome aberration

The PMN also was tested in an *in vitro* mammalian chromosome aberration assay, as

reported in "[redacted] *In vitro* mammalian chromosomal aberration test in Chinese hamster ovary cells," also conducted by [redacted] study dated July 25, 2007 (PMN Attachment 69). The PMN (purity as above) was tested both without and with metabolic activation using rat liver S9, as above. Dose selection was based upon the results of a Preliminary Toxicity Assay. The dose level of 3471 µg/ml, which represented 10mM, was the limit dose for this chemical in this assay. Two experiments were conducted. The first experiment involved exposure of the cells for four hours with 16h recovery, and was conducted without and with activation. Three dose levels of 1,000, 2,000 and 3,471 µg/ml were evaluated. The second experiment involved exposure for 20h with no recovery period, and was conducted without activation only. Three dose levels of 500, 1,000 and 2,000 µg/ml were evaluated. Cytotoxicity (>50%) was noted only at the highest dose in the 20hr treatment without activation. Dose selection was acceptable. Statistically significant increases in structural aberrations were detected for the 4h experiment with activation. No significant increases in structural aberrations were observed without activation, or in the 20h experiment either without or with activation, or for numerical aberrations under any test condition. Concurrent negative (sterile water) and positive controls (mitomycin C and cyclophosphamide for non-activated and activated assays, respectively) produced appropriate responses.

III. The *in vivo* micronucleus and chromosome aberration study

The PMN was tested for induction *in vivo* of micronuclei and chromosome aberrations, as reported in [redacted] In vivo micronucleus and chromosome aberrations assay in mouse bone marrow cells". The study was conducted by [redacted] study dated 10 October 2007 (PMN Attachment 92). The PMN (purity as above) was tested in male and female ICR mice. In a range-finding study, 4 of 5 male and 4 of 5 females died at 2,000 mg/kg body weight; in a subsequent study 1,300 mg/kg was determined to be the maximum tolerated dose. In the mutagenicity test proper, animals (5 males and 5 females per dose group) were exposed to three dose levels of 325, 650 and 1,300 mg/kg by a single oral administration (PO) and sacrificed 24 hours after exposure. Dose selection was acceptable. No significant increases in micronucleated polychromatic erythrocytes (mPCEs) or in chromosomal aberrations, either structural or numerical, were observed for any test condition. Concurrent negative (sterile water) and positive (cyclophosphamide) controls produced appropriate responses.

IV. *In vivo* Unscheduled DNA Synthesis (UDS)

The PMN also was tested for *in vivo* DNA effects in a UDS assay, as reported in "[redacted] Unscheduled DNA synthesis (UDS) test with mammalian cells *in vivo*", also conducted by [redacted] study dated 14 August 2007 (PMN Attachment 71). The PMN (purity as above) was tested in male rats exposed by oral gavage. Animals (5 males per dose group) were exposed to 500, 1,000 and 2,000 mg/kg body weight for 5 days/week, for 4 weeks, and harvest of animals occurred at 2-4h and at 12-16h after termination of exposure. Dose levels were based upon an initial rangefinding study, and were acceptable. No mortality was observed in the assay. No significant increases in net nuclear grain counts were observed. Concurrent negative (distilled water) and positive controls (dimethylnitrosamine) produced appropriate responses.

In summary, P08-509 is not a gene mutagen in two species of prokaryotes both without and with activation. It induces chromosomal mutations in mammalian cells *in vitro* in the form of structural

aberrations with activation but not without, and it does not induce numerical aberrations both without and with activation. It does not induce chromosomal mutations in mammals *in vivo* by the oral route in the form of structural aberrations, numerical aberrations, or micronuclei, nor DNA effects in the form of unscheduled DNA synthesis.

C) [redacted]

I. Bacterial reverse mutation

The test material was tested in a partial bacterial reverse mutation assay, as reported in "Mutagenicity testing of [redacted] in the *Salmonella typhimurium* plate incorporation test", conducted by [redacted], study dated November 10, 1994 (PMN Attachment 117). The PMN ([redacted]) was tested in *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535, both without and with metabolic activation using Aroclor 1254-induced rat liver S9. Since the study included only four bacterial strains instead of the usual five, it does not meet OECD or OPPT guideline requirements for the bacterial reverse mutation test. It was tested at seven dose levels ranging from 10.0 to 5,000.0 µg/plate, in triplicate plates per dose level. Dose selection was acceptable for a noncytotoxic chemical. There was no confirmatory study. The chemical did not induce significant increases in gene mutations under any test condition. Concurrent negative (the solvent, acetone) and positive controls produced appropriate responses.

II. *In vivo* micronucleus assay

The test material was tested in the *in vivo* micronucleus assay, as reported in "Combined two-week inhalation toxicity and micronucleus studies with [redacted] in rats". The study was conducted by [redacted], study dated September 21, 1995 (PMN Attachment 118). The chemical ([redacted]) was tested in male and female Crl:CD BR rats exposed by inhalation for 6h/day, 5 days/week for 2 weeks, to 5,000, 25,000 and 175,000 ppm of [redacted]. No systemic toxicity and no effect on bone marrow as defined by depression of the ratio of polychromatic to normochromatic erythrocytes were observed in the study. Dose selection was acceptable for a gaseous chemical. No significant increases in micronucleated polychromatic erythrocytes (mPCEs) were observed for any test condition. Concurrent negative (air) and positive controls (cyclophosphamide administered in a single intraperitoneal injection) produced appropriate responses.

In summary, [redacted] is not a gene mutagen in one species of prokaryote both without and with activation, although this study is considered incomplete. It does not induce chromosomal mutations in mammals *in vivo* by the inhalation route in the form of micronuclei.

D) [redacted]

I. *In vivo* micronucleus assay

The test material was tested in the *in vivo* micronucleus assay, as reported in "Combined two-week inhalation toxicity and micronucleus studies with [redacted] in rats". This is the same study as for chemical C above (PMN Attachment 118). The chemical [redacted] was tested in male and female Crl:CD BR rats by inhalation for 6h/day, 5 days/week for 2 weeks,

to one dose level, 25,000 ppm. The adequacy of the dose level cannot be determined since no systemic toxicity and/or no effect on bone marrow as defined by depression of the ratio of polychromatic to normochromatic erythrocytes was observed in the study. No significant increases in micronucleated polychromatic erythrocytes (mPCEs) were observed for any test condition, but these results are or uncertain value due to the question about the adequacy of the dose selection. Concurrent negative (air) and positive (cyclophosphamide) controls produced appropriate responses

In summary, [redacted] does not induce chromosomal mutations in mammals *in vivo* by the inhalation route in the form of micronuclei., but this study is considered inconclusive due to uncertainty about the adequacy of the dose tested.

E) [redacted]1

I. *In vitro* chromosome aberration

The test material was tested in an *in vitro* mammalian chromosome aberration assay, as reported in "*In vitro* evaluation of [redacted] for chromosome aberrations in human lymphocytes," conducted by [redacted], study dated December 19, 1994 (PMN Attachment 116). The test material was identified as [redacted]", ans was comprised of two components: [redacted]. It was tested both without and with metabolic activation using rat liver S9. Two experiments were conducted. The first experiment involved exposure of the cells for 3 hours, and harvest of cells 18-20 hours after the end of treatment. Five dose levels of 0.3, 1.0, 1.9, 2.9, 3.8 and 5.1 mg/ml (equivalent to 300, 1,000, 1,900, 2,900, 3,800 and 5,100 µg/ml) were applied. The highest four doses were used for mutagenicity evaluation. The second experiment was the same as the first, with an additional harvest of cells 24 hours after the initial harvest, at the same dose levels as for the first experiment. Again the four highest surviving doses were used for mutagenicity evaluation. Dose selection was acceptable. Without activation, there were statistically significant increases in structural aberrations at the two highest doses in the first experiment and at the second highest dose (3.8 mg/ml) in the second experiment; with activation there were statistically significant increases at 1.9 and 2.9 mg/ml in the first experiment and at 1.9 and 3.8 mg/ml in the second experiment. Cells from the additional harvest time for the second experiment were not evaluated since positive responses had already been obtained for the earlier harvests. Concurrent negative (acetone) and positive controls (mitomycin C and cyclophosphamide for non-activated and activated assays, respectively) produced appropriate responses.

In summary, the analogue [redacted] induces chromosomal mutations in human cells *in vitro* in the form of structural aberrations both without and with activation.

There are mutagenicity data available on analogues of the PMNs. These have been recently reviewed for [redacted]. The structures for these analogues are also in Section II. The mutagenicity data are summarized as follows:

[redacted]

The data on PMNs 08-508 and -509, its three transformation products, and four other analogues, are summarized in the Table on the next page:

TABLE: MUTAGENICITY DATA ON P08-508, -509 AND ANALOGUES

Chemical	Gene mutations		Chromosome mutation				DNA
	SAL	E.coli	cytogenetics mam vt		MN vv	CA vv	UDS
			CA struc	CA num			
P08-508	neg wo & w	neg wo & w	neg CHO wo & w	pos CHO wo & w			
P08-509	neg wo & w	neg wo & w	pos CHO w & neg wo	neg CHO w & wo	neg m&f mou PO	neg m&f mou PO	neg UDS m rat PO
[redacted]	inc neg wo & w				neg MN m rat inh		
[redacted]					inc neg MN m rat inh		
[redacted]			pos hum lymp wo & w				
[redacted]	neg wo & w	neg wo & w	pos CHL wo & w				
[redacted]	neg wo & w	neg wo & w					
[redacted]	neg wo & w	neg wo & w					
[redacted]	neg wo & w	neg wo & w					

Abbreviations used in Table:

CA = chromosomal aberrations; CHL = Chinese hamster lung fibroblasts; CHO = Chinese hamster ovary cells; E.coli = *Escherichia coli*; f = female; hum lymp = human lymphocytes; inc = inconclusive; inh = inhalation
m = male; mam = mammalian cells; MN = micronuclei; mou = mouse; neg = negative; num = numerical aberrations; PO = oral gavage; pos = positive; SAL = *Salmonella*; struc = structural aberrations; UDS = unscheduled DNA synthesis; vt = *in vitro*; vv = *in vivo*; w = with activation; wo = without activation

Thus, based upon data on the PMNs themselves and on analogues, P08-508 and P08-509 are or may be: (a) not gene mutagens in two species of prokaryotes; (b) chromosome mutagens in mammalian and human cells in culture, but not in mammals *in vivo* and; (c) not inducers of DNA effects in mammalian cells *in vivo*.

The positive responses for chromosome aberrations *in vitro* for polyploidy in CHO cells [redacted]

[redacted]), for structural aberrations in CHO cells (P08-509), for structural aberrations in human cells [redacted], and for aberrations in CHL cells [redacted]), are of some concern. However, the negative responses in *in vivo* chromosomal assays for micronuclei and for chromosomal aberrations PO (P08-509), and for micronuclei by inhalation [redacted]), alleviate the concern. In addition, there is negative evidence that P08-509 induces DNA effects (UDS) *in vivo*.

Due to these *in vivo* results, there is no basis for recommending additional mutagenicity testing for the PMNs 88-508 and -509, and there is little support for a cancer concern based upon mutagenicity. The negative mutagenicity concern does not negate a cancer concern should such concern be based upon nongenotoxic information.

IV. REFERENCE

Cimino, MC. 2008. U. S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. Mutagenicity Hazard Review of [redacted]. Intradivision memorandum to S Cragg, dated January 18, 2008. USEPA. Washington, DC 20460.

MEMORANDUM

From: Yin-tak Woo
To: Steve Cragg
Thru: Don Rodier
Re: Abbreviated Note on Cancer Concern on P08-508 and P08-509

[redacted]

The two PMN chemicals, P08-508 and P08-509 are structurally related to perfluoro-octanoic acid (PFOA). Submitted data showed that both chemicals have no significant mutagenic activity and no evidence of metabolism under *in vitro* conditions. The 98% clearance time after oral administration was 22-28 hr in male rats and 4-8 hr in female rats for P08-508 and 12-22 hr in male rats and 4-8 hr in female rats for P08-509. The half life (50% clearance time) of the chemicals could not be calculated from the data but should be less than the 98% clearance time. For comparison, the half life of PFOA was 138-202 hr in male rats and 2.8-16 hr in female rats (OPPT, 2005). It appears that the same gender difference in clearance of P08-508 and P08-509 was observed and that the clearance time for both P08-508 and P08-509 should be substantially lower than that of PFOA in male rats.

Although PFOA has been shown to be carcinogenic, the concern for the cancer endpoint is substantially lower than that of developmental toxicity or immunotoxicity. PFOA has been/was given a *suggestive evidence* classification by EPA (OPPT, 2005). The SAB was indecisive with respect to whether PFOA should be suggestive or likely. PFOA has three cancer targets in male rats (liver, Leydig cells of the testis, acinar cells of the pancreas); the evidence is equivocal in female rats. The liver tumors are believed to be the result of activation of the peroxisome proliferator activated alpha receptor (PPARα) whereas the Leydig cell tumors are hypothesized to be associated with an increased level of serum estradiol in concert with testicular growth factors. Both of these modes of action are believed to be of insignificant or questionable human relevance. The mode of action of the induction of pancreatic acinar cell tumors remains to be studied; however, such tumors are rare in humans. No cancer risk assessment has been conducted by EPA. An earlier OPPT attempt of risk assessment of PFOA using mammary tumors was abandoned after the pathology re-reading of the slides changed the tumor incidence of the control group and obliterated the statistical significance. Since available data indicate that the carcinogenic action of PFOA appears to be receptor-mediated, the faster clearance of P08-508 and P08-509 may suggest that the carcinogenic potential of these two chemicals should be lower than PFOA.

In conclusion, P08-508 and P08-509 are structurally related to PFOA and share common toxic and metabolic profile. However, the clearance time of both PMN is substantially lower than that of PFOA in male rats. The human cancer concern of these two PMN chemical is expected to be at best suggestive or marginal and most likely lower than that of PFOA.

OPPT: Draft Risk Assessment of the Potential Human Health Effects Associated with Exposure to Pefluorooctanoic Acid and its Salt. January 4, 2005. (http://www.epa.gov/opptintr/pfoa/pubs/pfoarisk.pdf)

J:\POSTFOCU\FY2008\P080508c.sr\P080508c_ICB.doc

EETD STANDARD REVIEW REPORT
- ICB Chemistry Section -

Case Number: P-08-0508 / 0509 **CBI:** [redacted]
Chemist: Greg Fritz
Due Date: 08/11/2008

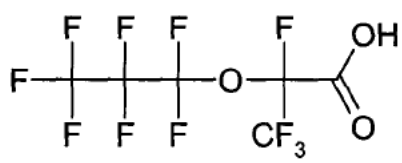
Submitter: DuPont
Production Volume: [redacted] 508 / 509

CA Index Name: Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)- 508 / Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-, ammonium salt (1:1) 509

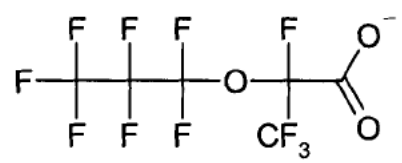
CASRN: [13252-13-6] 508 / [62037-80-3] 509

Categorical Name: PFAC ether & salts

Chemical Structure:



508



509

P-Chem. Properties and Analysis:

MF: [redacted]	**MF:** [redacted]
MW: 330	**MW:** 347
MP:	**MP:** [redacted] ǂ
BP: [redacted]	**BP:**
VP: [redacted]	**VP:**
log Kow: NA-surfactant	**log Kow:** NA-surfactant
Sol H_2O: infinite	**Sol H_2O:** infinite
pKa: 3	

*

- MSDS [redacted]
- Lit. BP 60 °C @ 10 mm Hg Alfa Aesar MSDS
- Lit. BP 186 – 188 °C Matrix Scientific Catalog
- Independent lab 129 °C DuPont pre-PMN communication

ǂ MP, BP, VP for ammonium salt were performed on aq. sol'n and neat info is currently being

measured. [redacted]

Manufacturing process:

[redacted]

(P-08-508)

[redacted]

Use: The PMN substance (508) will be used exclusively as an [redacted]

The submitter also states that the sale of the PMN materials to other companies is under consideration, but no commitments have been made.

Technical Considerations for PMN Substance: The principle concern is the exposure to this new polymerization aid. DuPont takes great pains to recover / destroy the 509 used as a polymerization aid. [redacted]

[redacted]

Half-Life of Rf-COOH Conversion to Thermolysis Product Rf-H		
Product / Temp.	**150 °C**	**200 °C**
P-08-0508	**2500 sec**	**1900 sec**
P-08-0509	**500 sec**	**200 sec**

The attachment 66 appears to indicate that [redacted] that would readily destroy the [redacted] converting it into the Rf-H thermal byproduct in seconds.

Most other solid products are exposed to [redacted] Based on data [attachment 45B and 66 in PMN document]indicates that the [redacted] exposed to condition where [redacted] Dupont was asked :

1) What % of product is subject to these lower temperatures? [redacted]
2) Are there additional thermal treatment that would convert untreated [redacted] into Rf-H? [redacted]
3) What is the expected level of conversion into Rf-H as % of [redacted] present? [redacted]

Working backwards one sees that a reduction in T by 50 °C [redacted] more than doubles the residence time for half life. So at 70 °C one would expect the half life to be at least 2000 seconds. Furthermore, [redacted] into Rf-H but the half life of the free acid is 10 fold that of the ammonium salt; one may postulate that the activation energy barrier must be overcome to cleave the C-C bond which may take the higher temperature. [redacted] Conversion to Rf-H below 150 °C may not occur. Krusik & Roe noted APFO showed no decomposition below 196 °C [Anal. Chem. 2004 (76) 3800]. At 150°C, for 509 50% conversion would occur in about 10 minutes. The engineering report should give releases during the polymer manufacturing in general as well as product content.

[redacted]

P-Chem Properties of the Rf-H Thermal Degradation Product:

MF [redacted]
MW: [redacted]

MP: < -55 (limit)
BP: 49 °C
VP: 30,100 Pa (226 mm Hg)
log Kow: 3.83 est (BAD estimate)
Sol H_2O: 7.07 mg/L

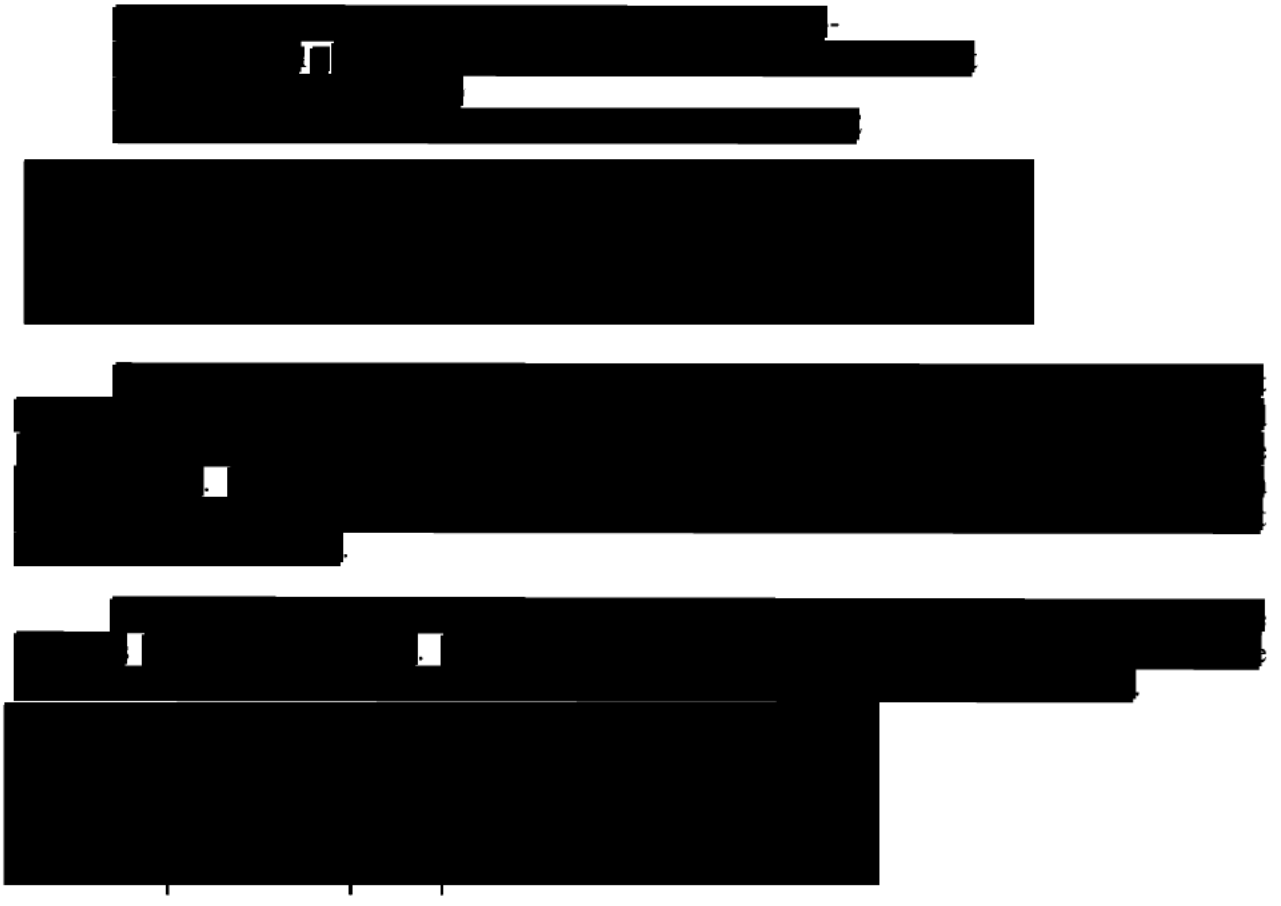
[redacted]

Alternative Uses: The only listed use for these chemical substance is as an intermediate [508] for [redacted] aid [509]. The caustic nature of the highly acidic 508 will limit its uses to that of intermediate. But the low surface tension of fluorinated acids would possibly lead to other salts [Na, K, Li, Me4N+, etc....] which could act as surfactants for a variety of applications (hard surface cleansers, paints & coatings, floor wax, photographic dispersions, paper & ink coatings, etc...).

Analogs:

[redacted]

Normally the diacids are substantially different chemically [more water soluble, less volatile, higher MW]. Of interest, however, these products appear to be more of a concern physiologically than the chemical differences can account for. Perhaps, in the aq. bloodstream the tendency to form micelles is similar to the PMN substance and therefore the 2 compounds have similar properties and chemical reactivity when dispersed. The fraction of product that has C8 – C16 becomes less like the PMN substance which is a C6 analog.



Recommendation: As it stands now, this new substance appears to have an immediate advantage to [redacted] and maybe could alleviate fears from [redacted] releases, but the uncertainty surrounding the fluoroethers issue makes it as attractive as other Rf lower homolog alternatives. There appears to be evidence that the PMN substance decarboxylates upon heat treatment. On the downside there is some transport of the PMN substance via sublimation mechanism.

The disadvantage is that the uncertainty of the toxicity and PBT characteristics may not be substantially better than the [redacted] Although the retention in animals exposed to PMN substance appears to favor quick excretion favoring lower exposure times.

References: See text above.

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0508
Standard Review Draft 9/3/2008

ENGINEER: El-Zoobi \ CLM
PV (kg/yr): [redacted]

SUBMITTER: DuPont

USE: [redacted] intermediate [redacted] and [redacted] polymerization aid [redacted]. [redacted]

OTHER USES: [redacted]

MSDS: Yes Label: No

Gen Eqpt: Use only with adequate ventilation. Keep container tightly closed. // Coverall splash goggles; face shield where possibility exists for face contact due to splashing or spraying of material. // Impervious gloves, apron, pants, and jacket (Neoprene material)
Respirator: NIOSH approved positive pressure air-supplied respirator in situations where the product may become airborne.
Health Effects: Causes skin burns // Corrosive, may cause permanent eye injury // Causes respiratory tract irritation // Causes severe digestive tract burns.
TLV/PEL:
none established

CRSS (07/10/2008):
Chemical Name: Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-
S-H20: 0.043 g/L @
VP: [redacted] @
MW: 330.06 %<500 %<1000
Physical State and Misc CRSS Info:
Neat: [redacted] NA End Use: Destroyed.
Submitted data: [redacted]. Estimated data: NOMO5 for [redacted] bp = 172.7°C at 760 torr, vp = 1.8 torr. ACD Labs (Prop Database): bp = 187.5°C, vp = 0.28 torr, ws = 0.043 g/l, log P = 8.12. EPI (with mp entered as 20°C): bp = 186.9°C, vp = 0.691 torr, ws = 0.205 torr, log P = 3.66.

Consumer Use: No

SAT (concerns) (07/11/2008):
Related Cases and Related Cases and Misc SAT Info:
RELATED CASES: [redacted]
Migration to groundwater: Rapid

PBT rating: P3B2T3 .
Health: 2-3 Dermal, Drinking Water, Inhalation, Ingestion
Eco: 2 Water (All releases to water with a CC = 1000 ppb)

OCCUPATIONAL EXPOSURE RATING: 2-3B

POLLUTION PREVENTION CONSIDERATIONS:
P2 Claim: DuPont developed the PMN substance used in polymerization process as a low toxicity, rapid bio-elimination

EXPOSURE-BASED REVIEW: No

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0508

Manufacturing

Number of Sites/ Location [redacted]
Days/yr: [redacted]
Basis: Submission specifies [redacted]

[redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY
IRER Note: The daily releases listed for any source below may coincide with daily releases from the other sources to the same medium.

[redacted]

OCCUPATIONAL EXPOSURES ESTIMATE SUMMARY

[redacted]

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0508

Use: [redacted]

Number of Sites/ Location: [redacted]

Days/yr: [redacted]

Process Description: [redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

[redacted]

RELEASE TOTAL

[redacted]

OCCUPATIONAL EXPOSURES ESTIMATE SUMMARY

[redacted]

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0508

Further Use 1a: [redacted]

Number of Sites/ Location: [redacted]

Days/yr: [redacted]
Basis: [redacted]

Process Description: [redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

[redacted]

lease [redacted]

[redacted]

[redacted]

[redacted]

[redacted]lease [redacted]

[redacted]

[redacted]

lease [redacted]

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0508

Further Use 2: [redacted]

Number of Sites/ Location: [redacted]

Days/yr: [redacted]

Process Description [redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0508

Further Use 3: [redacted]

Number of Sites/ Location: [redacted]

Days/yr: [redacted]

Process Description: [redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

Dermal:

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0508

Further Use 1b: [redacted]

Number of Sites/ Location: [redacted]
Days/yr: [redacted]
Basis: [redacted]

Process Description: [redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

Dermal:

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0508

Releases from [redacted]

Number of Sites/ Location: [redacted]

Days/yr: [redacted]

Process Description: [redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

[redacted]

MEMORANDUM of [redacted] TELEPHONE CONVERSATION

CALL BY: Casey MacQueen
Organization: ERG

CALL TO: Jane Bradd Andersen

Organization: Submitter

Date: 07/16/2008

Time: 11am

Phone: [redacted]

Concerning what TSCA CBI?

PMN: 08-0508

[redacted]

[redacted]

[redacted]

MEMORANDUM of [redacted] TELEPHONE CONVERSATION

CALL BY: m. el-zoobi
Organization: epa

CALL TO: Jane Bradd Andersen, [redacted]

Organization: Submitter

Date: 08/29/2008

Time: 8

Phone: [redacted]

Concerning what TSCA CBI?

PMN: 08-0508

[redacted]

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0509
Standard Review Draft 9/23/2008

ENGINEER: [redacted]
PV (kg/yr): [redacted]

Revision Notes / Assessment Overview: [redacted]

SUBMITTER: DuPont

[redacted]

MSDS: Yes Label: No

Gen Eqpt: Use only with adequate ventilation. Keep container tightly closed. // Coverall splash goggles. Face shield where possibility exists for face contact due to splashing or spraying of material. // Impervious gloves, apron, pants, and jacket (neoprene).
Respirator: NIOSH approved positive pressure air-supplied respirator in situations where the product may become airborne.
Health Effects: May irritate skin. Corrosive, may cause permanent eye injury. Repeated exposure may alter blood chemicstry.
TLV/PEL:
none established

CRSS (07/10/2008):
Chemical Name: Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-, ammonium salt (1:1)
S-H20: Dispersible g/L @
VP: [redacted]
MW: 347.09 %<500 %<1000
Physical State and Misc CRSS Info:
Neat: Solid Mfg: [redacted]

[redacted] =

Consumer Use: No

SAT (concerns) (07/11/2008):
Related Cases and Related Cases and Misc SAT Info:
RELATED CASES: [redacted]
Migration to groundwater: Rapid
PBT rating: P3B2T3 .
Health: 2-3 Dermal, Drinking Water, Inhalation, Ingestion
Eco: 2 Water (All releases to water with a CC = 1000 ppb)

OCCUPATIONAL EXPOSURE RATING: [redacted]

NOTES & KEY ASSUMPTIONS:

[redacted]

[redacted]

POLLUTION PREVENTION CONSIDERATIONS:

[redacted]

EXPOSURE-BASED REVIEW: No

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0509

Manufacturing: (from P08-0508)

Number of Sites/ Location: [redacted]

Days/yr: [redacted]
Basis: [redacted]

Process Description: [redacted]
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)

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

[redacted]

[redacted]

INITIAL REVIEW ENGINEERING REPORT
PMN: 08-0509

Use: [redacted]

Number of Sites/ Location: [redacted]

Days/yr: [redacted]

Basis: [redacted] 5.

Process Description: [redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] to [redacted]

[redacted]

[redacted]

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0509

Use: [redacted]

Number of Sites/ Location: [redacted]

Days/yr: [redacted]

Basis: [redacted]

Process Description: [redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

[redacted]

OCCUPATIONAL EXPOSURES ESTIMATE SUMMARY

[redacted]

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0509

Use: [redacted]

Number of Sites/ Location: [redacted]
unknown site
Days/yr: [redacted]
Basis: [redacted]

Process Description: [redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

[redacted]

OCCUPATIONAL EXPOSURES ESTIMATE SUMMARY

[redacted]

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0509

Further Use, Scenario 1: [redacted]

Number of Sites/ Location: [redacted]
unknown site(s)
Days/yr: [redacted]

Process Description: [redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

[redacted]

OCCUPATIONAL EXPOSURES ESTIMATE SUMMARY

[redacted]

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0509

Further Use, Scenario 2: [redacted]

Number of Sites/ Location: [redacted]
Days/yr: [redacted]
Basis: [redacted]

Process Description: [redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

OCCUPATIONAL EXPOSURES ESTIMATE SUMMARY

[redacted]

INITIAL REVIEW ENGINEERING REPORT [redacted]
PMN: 08-0509

[redacted]

Number of Sites/ Location: [redacted]

Days/yr: [redacted]

Process Description: [redacted]

ENVIRONMENTAL RELEASES ESTIMATE SUMMARY

[redacted]

[redacted]

MEMORANDUM of [redacted] TELEPHONE CONVERSATION

CALL BY: Jane Bradd Andersen
Organization: Dupont

CALL TO: m. el-zoobi

Organization: epa

Date: 09/04/2008

Time: 2

Phone: [redacted]

Concerning [redacted] ?

PMN: 08-0509

[redacted] Q3:

POST FOCUS EXPOSURE REPORT

This report is a revised version of the original exposure report for **this P3B2 chemical, P080509.**

Results Table: Dose, Concentration, and Days Exceeded Results Summary

Exposure Scenario[1]	Water						Land fill	Stack Air		Fugitive Air	
Release activity(ies)[2]; exposure calculation(s)[3]	Drinking Water		Fish Ingestion		7Q10 CC=4	PDM Days Exceeded	LADD	ADR	LADD	ADR	LADD
	ADR	LADD	ADR	LADD							
	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	µg/l	# Days	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
Mfr/Use/Proc, PDM1 max ADR	**2.74E-06**		**5.26E-08**		**4.41E-02**	**0**	-	-	-	**0.46**	-
Mfr/Use/Proc, PDM2					**4.01E-02**	**0**	-	-	-	-	-
Mfr/Use/Proc, max LADD		**2.38E-09**		**3.23E-10**			-	-	-	-	**4.81E-03**
Use 2 PDM, ADR	**1.98E-07**		**6.16E-09**		**3.65E-03**	**0**	-	-	-	-	-
Use2, Max ADR	**2.92E-06**		**9.08E-08**								
Use2, Max LADD		**4.34E-09**		**5.88E-11**			-	-	-	-	-
Use 3, ADR, PDM1	**1.19E-05**		**3.05E-07**		**0.19**	**0**	-	-	-	-	-
Use3, PDM2,max ADR	**8.11E-03**		**1.85E-04**		**166.24**	**0**	-	-	-	-	-
Use3, max LADD		**4.74E-05**		**6.42E-07**			-	-	-	-	-
Use 3, PDM3, ADR	**6.22E-04**		**1.42E-05**		**12.76**	**0**					
Use 4, PDM, max ADR	**3.84E-05**		**8.75E-07**		**0.79**	**0**					
Use 4, max LADD		**8.20E-07**		**1.11E-08**							
Use 6, max ADR										**2.76E-02**	

[1] Exposure scenario titles consist of release activity followed by exposure calculation abbreviation.
[2] Release activities are from engineering report's Manufacturing (Mfg), Processing (Proc) and Use release activity labels. Multiple release activities are combined in one exposure scenario if their releases occur at same location.
[3] Exposure calculations are Acute Dose Rate (ADR), Lifetime Average Daily Dose (LADD), and Probabilistic Dilution Model (PDM). There may be one, two, or all three exposure calculations per exposure scenario.

CC is the aquatic concentration of concern.

Results Table: Exposure Based (XB)/Persistent (P2B2) Criteria

[redacted]

Summary Economic Analysis
For Standard Review of PMN P-08-508/509
Reviewer: Wendy Hoffman

I. BACKGROUND

A. Submitter: DuPont, Inc.

B. Chemical Names: **P-08-508:** Propanoic acid, 2, 3, 3, 3-tetrafluoro-2-(1, 1, 2, 2, 3, 3, 3-heptafluoropropoxy)-
P-08-509: Propanoic acid, 2, 3, 3, 3-tetrafluoro-2-(1, 1, 2, 2, 3, 3, 3-heptafluoropropoxy)-, ammonium salt (1:1)

C. Generic Names: **P-08-508:** Perfluorinated aliphatic carboxylic acid
P-08-509: Perfluorinated aliphatic carboxylic acid, ammonium salt

D. Trade Names: Not applicable

E. CAS Numbers: **P-08-508:** 13252-13-6
P-08-509: 62037-80-3

F. Use(s): **P-08-508:** [redacted]
P-08-509: [redacted]

G. Production Volumes: **P-08-508:** [redacted]
P-08-509: [redacted]

H. Selling Prices: **P-08-508:** [redacted]
P-08-509: [redacted]

II. MARKET ANALYSIS

A. Intended Uses:

According to the PMN, 508, [redacted]

[redacted]

The submitter confirmed by phone that the company is not aware of any other uses for the substances, including no consumer uses or other industrial uses.

The PMN substances will [redacted]

According to the submitter, the [redacted] made using the PMN substances will have the same end uses as the [redacted] currently made with [redacted].

B. Submitter:

[redacted]

C. Substitutes:

According to the submitter, the PMN substances are replacements for the use of [redacted]

According to the submitter, the 509 substance is not a drop-in replacement for [redacted]. The [redacted] recipe will change when the switch is made to 509. The changes will be in the operating conditions for the manufacture of [redacted] and control technologies. The goal is to have the [redacted] manufactured using 509 be the same as [redacted] manufactured using [redacted].

[redacted]

D. Benefits of the PMN Substance:

According to the PMN, the PMN substances will enable DuPont to phase-out its manufacture and use of [redacted]. The submitter stated that the reason for making the PMN substances is so that DuPont can get out of the [redacted]. According to the PMN, in comparison to [redacted], the PMN substances are low toxicity and are eliminated rapidly from mammals. In addition, according to the PMN, the manufacturing and use processes for the PMN substances have been engineered to minimize environmental emissions and exposure. The submitter confirmed that information and had nothing further to add about benefits of the PMN substances.

E. Production Volume and Market Trends:

[redacted]

The only markets for the substances that DuPont sees are as a [redacted] polymerization aid. The submitter emphasized that DuPont's goal is to recapture and recycle as much of the 509 substance as possible, so that it would have to make less and less virgin 509 over time. They are still having some technical difficulties with the capture technology, but they hope to have the problems resolved soon.

[redacted]

F. Selling Price

[redacted]

[redacted]

Telephone Log – PMN P-08-508/509

DATE: August 27 and September 3, 2008

EPA STAFF: [redacted]

RESPONDENT: Jane Bradd Andersen, the DuPont Company

The EPA staff member contacted the submitter's technical contact to request information concerning the chemicals described in the PMN to complete the economic report for the standard review. The conversation has been paraphrased for brevity and clarity.

Q1(a): Can you confirm the information in the PMN that 508 is going to be used as [redacted] (509), and that 509 is [redacted]

A1(a): Yes, I can confirm the use information in the PMN.

Q1(b): Can you confirm the production information in the PMN regarding internal, external and export uses for the PMN substances?

A1(b): [redacted]

Q1(c): Regarding PMN Attachment 113 – [redacted]: Can you tell me why only use information [redacted] was included in the PMN, and not other [redacted] formulations?

A1(c): The information on [redacted] uses was included in response to a request from EPA.

Q1(d): Are there any other uses that the PMN substance could work in, even if you aren't planning on them now? Can you confirm that there are no consumer or commercial uses?

A1(d): We are aware only of the substances' uses as polymerization aid ([redacted] to [redacted], and have no intentions of using them in any other way. Yes, I can confirm that there are no consumer or commercial uses. The [redacted] made using the PMN substances will have the same end uses as the [redacted] currently made with [redacted].

Q2: The PMN states that the PMN substances will be used as a [redacted]. Can you confirm that? [redacted]

A2: Yes, I confirm that the PMN substances will be used only as a [redacted]. That was our purpose in developing the products. Our goal is to get out of the [redacted]

Q3: Can you tell me about the benefits of the PMN substance relative to [redacted] In terms of toxicity, persistence, environmental effects, etc. What about the manufacture and use processes -- environmental benefits as described in the PMN, including capture and recycle technology?

A3: The benefits of the substances are discussed in the PMN attachment. The PMN substances will enable DuPont to [redacted]. We developed the PMN substances to have low toxicity and rapid bioelimination from mammals [redacted]. We engineered the manufacturing and use processes for the PMN substances to minimize environmental emissions and exposure. They were also developed to be recaptured and recycled. Our goal is to make as little virgin material as possible, and recapture and recycle increasing amounts of the substances. We are still working on the recapture/ recycle technology.

Q4: Can you confirm the information in the PMN that your company will be manufacturing 508 at your [redacted], and will be manufacturing 509 at your [redacted]

A4: Yes, I can confirm that we will be manufacturing 508 at our [redacted]

Q5: Do you have any plans to manufacture either substance at any other U.S. facility, DuPont-owned or otherwise? What about importing?

A5: [redacted]

Q6: [redacted]

A6: Yes, I can confirm that production volume information.

Q7: How much 509 is needed [redacted]?

A7: [redacted]

Q8: The PMNs says 509 is not a [redacted]. Can you explain how it will be used differently?

A8: That is correct. The 509 substance is not a [redacted].

Q9: How do you see the market growth potential for the PMN substances after the third year?

A9: [redacted]

Q10: Can you tell me anything about the customer who might use 509 to make [redacted]? Is that company a [redacted] manufacturer? Do you have any other potential customers lined up for either 508 or 509?

A10: [redacted]

Q11: Can you tell me the selling price per kilo for the PMN substance on a 100 percent PMN-substance basis? How does this compare with the PFOA price?

A11: [redacted]

Q12: Would you like to add any other information?

A12: No, thank you.

The EPA staff person thanked the submitter for her cooperation.